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Editorial

Current healthcare system in Japan: Current issues and future directions

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Abstract:
Japan's healthcare system recognized for its achievements in universal healthcare coverage, for one of the highest life expectancies, and for low infant mortality rate. These impressive results achieved after decades of thoughtful policy making process and financial investments into the equitable access. In addition to that Japan has a long history of strong public health traditions and sophisticated insurance model. On the other hand, despite these achievements, the healthcare system recently faces growing pressure which may impact its sustainability and fairness. One of the challenges is rapid aging of population. In combination with persistently low fertility, these challenges are reshaping the demand for healthcare and long-term care services. Moreover, financial pressure in increasing with health-related and social security expenditures consume a growing share of the national budget. A shrinking number of workforces, unequal healthcare provider distribution, and fragmentation across nearly 3,000 health private insurers create additional inefficiencies and threaten equitable access of the population to healthcare services, especially in the rural areas. In addition, the healthcare system is under strain from rising number of multimorbidity and increasing mental health issues among young population. Advance in technological progress creates opportunities but at the same time requires substantial adaptation.

Keywords: Japan; Healthcare Challenges; Insurance

Introduction

Japan's healthcare system recognized for its achievements in universal healthcare coverage, for one of the highest life expectancies, and for low infant mortality rate. These impressive results achieved after decades of thoughtful policy making process and financial investments into the equitable access. In addition to that Japan has a long history of strong public health traditions and sophisticated insurance model. On the other hand, despite these achievements, the healthcare system recently faces growing pressure which may impact its sustainability and fairness. One of the challenges is rapid aging of population. In combination with persistently low fertility, these challenges are reshaping the demand for healthcare and long-term care services. Moreover, financial pressure in increasing with health-related and social security expenditures consume a growing share of the national budget. A shrinking number of workforces, unequal healthcare provider distribution, and fragmentation across nearly 3,000 health private insurers create additional inefficiencies and threaten equitable access of the population to healthcare services, especially in the rural areas. In addition, the healthcare system is under strain from rising number of multimorbidity and increasing mental health issues among young population. Advance in technological progress creates opportunities but at the same time requires substantial adaptation.

This editorial provides short overview of these interrelated challenges and explores some possible practical policy directions. Another purpose of this paper is to highlight demographic, financial, organizational, and technological issues that maybe helpful for policy-makers, providers, and researchers on how Japan can adapt its system while maintaining its commitment to equity, quality, and universal health coverage. The current experience and lessons from Japan will not only shape its own future but also offer valuable insights for other countries which experiences similar demographic and financial issues. The following are the main current challenges:

1. Growing demographic and long-term care demands. Japan has one of the world's largest proportions of aged population due to low fertility rate and constantly rising life expectancy (1). As of 2023, Japan's recently decreasing population reached about 124.4 million, with nearly one in three of them (31.7%) aged 65 or older. Demographic prognosis predicts a highly possible scenario of decline to around 105 million people by 2050 (2). Socioeconomic factors such as postponed marriage, growing numbers of unmarried individuals, changes in household structures, and restrictive immigration policies influence to this worrying demographic changes (3-5). As a result of increased proportion of elderly population healthcare system already experiences growing demand on chronic disease management. In addition to that elderly people who need support put additional demand on long-term care (LTC) systems, and family caregivers. Local governments facing increasing social burdens to provide adequate elder care. It also worth to mention that average age of caregivers in nursing care facilities is above 50 years old.
2. Rising healthcare financial spending and financial stability. In Japan spending on social welfare, which includes healthcare and long-term care has gradually grow up, rising from 15% of total expenditure in 1995 to 20% in 2014, and reached 26% in 2021 (6). In 2023, healthcare spending **was 10.74% of GDP (7)**, slightly higher the OECD average of 9.2% (8). One-third of the national budget is spent to social security, which includes significant amounts for healthcare, pensions, and long-term care (6). The decline of working-age population has led to reduction in social insurance and placing additional contributions, putting further pressure on the National Health Insurance (NHI). Imbalance in financial volume across municipalities and disintegration among nearly 3,000 insurance companies contribute to ineffectiveness and inequality (6). Without reforms to improve system integration, strengthen cost control, and secure new revenue sources, securing the sustainability of universal health coverage will be challenging.
3. Workforce shortages and unequal distribution. Growing demand of nurses, primary care doctors, and long-term care staff is leading to their constant shortage. The gap in the distribution of medical doctors and nurses between urban and rural areas which was an issue for many decades recently become more wider despite the increase in the total number of health workers (9). Reimbursement policies on securing high payment which stimulated by emergency care hospitals in urban areas to increase nurse-per-bed ratios even more skew nurses' allocation distribution (10). For example, in Tokyo, shortages of long-term care workers are even more noticeable because of the competition with other service industries and greater wage differences compared to other regions (11). Long-term care providers across the country

deal with low wages, high staff turnover, and insufficient training channels, leading to predicted shortage of up to 130,000 nursing personnel by 2025 (6). Workforce ageing and rising burnout further undermine service continuity and system resilience, threatening equitable access to care across regions.

4. Fragmentation of health insurance and primary care capacity. Besides National Healthcare coverage, Japan also characterized by fragmented private health insurance plans, with nearly 3,000 separate insurers with varying premium rates, and a hospital-centric service model. Japanese healthcare does not have a distinct gatekeeping system like family doctors. In general, the referral letter is needed to access secondary and tertiary care, but is some cases patients may have a direct access which lead to overuse of hospital outpatient departments. Recent policies require patients without referral letters to pay an additional fee at large hospital, but distinctions between primary and secondary care remain blurred (6). This not well-structured primary care coordination contributes to inefficiencies in chronic disease management and constrains of acute-care resources.
5. Limited interoperability of medical records. Introduction of electronic medical records (EMRs) to the hospitals was well accepted and quickly expanded, with 27.3% of hospitals implementing them by 2014. On the other hand, interoperability of patients' data across institutions remains highly limited. The reason of such situation is due to high implementation costs and public concerns over data privacy concerns. (6). So, this fragmented health information environment greatly limit population health data management, reduces effectiveness of real-time surveillance, and limits the use of data for evidence-based resource allocation.
6. Burden of multimorbidity and mental health issues. Multimorbidity is condition when two or more chronic illnesses affect health and quality of life. Multimorbidity being common in middle age increases sharply after age 60. In Japan this condition is mainly linked to complex social determinants such as unemployment and socioeconomic disadvantage (10). Multimorbidity complicates clinical management and emphasizes the need for integrated healthcare models that address both medical and social factors. At the same time, growing number of mental health conditions remain underdiagnosed and as a consequence – undertreated. Mental health conditions often associated with persistent stigma, long working hours, and occupational stress. *Karoshi* (death from overwork) and work-related suicides highlight the scale of the challenge, while gaps in community-based mental health services and workforce shortages hinder timely and effective care.

Future perspectives and policy directions:

1. Enhance community-based integrated care. One of successful primary health care features is integrated health care stated in Astana declaration (13). The Japanese government proposed the establishment of a community-based integrated care system by 2025 to ensure comprehensive provision of health care, nursing care, preventive care, housing, and livelihood support (14). It involves addressing the lack of clear coordination between providers. Is also addresses unclear assignment of responsibilities. New models should connect primary care, social services, and long-term services. The focus should be made on multidisciplinary teams, proactive case management for high-risk patients, and expansion of home- and community-based services to reduce unnecessary hospitalizations.
2. Improve financing and payment incentives. As Japan's health care and long-term care costs are climbing up, so the payment reform will be required to make system more secure. The current financial arrangement relies mainly on social insurance contributions supported by large portion of tax-based subsidies, putting more strain on the national budget. There are differences between municipal National Health Insurance (NHI) schemes and Employees' Health Insurance when people with lower and unstable income (e.g., freelancers, unemployed) often pay higher premiums relative to income than full-time workers which highlight inefficiencies and inequities. It is possible to reduce such inequalities by using blended provider-payment models. This would include capitation with quality metric, bundled payments for managing chronic conditions and targeted incentives for prevention. This could lead providers pay attention on behavior with outcomes rather than service volume (15).
3. Allocate resources for health workforce and launch task-shifting strategies. To address the labor shortage

in Japan, the government needs invest significant funds in training and improving staff retention strategies. Making certification system more flexible so that workload in a clinical setting would be more evenly distributed. Employing more nurse practitioners and physician assistants can help compensate the shortage of medical doctors, especially in primary care and long-term care facilities. Targeted recruitment strategies are crucial for rural areas, including financial incentives, remote surveillance, and rotational employment, to address the improper placement of service providers (13). Without these steps, predicted shortages, along with high staff turnover, aging staff, and wage competition in cities, will reduce equity and access to health care.

4. Accelerate advancement of digital health and the integration of data. Japan needs to consider to establish nationwide standards for interoperability and the secure sharing of medical information in order to further improve public health service. Creating reliable and robust real-world data platforms will make possible predictive analytics and help stakeholders to response quickly in case of infectious disease outbreaks. At the same time, adequate protection of people's personal data during handling of digital information is essential. Japan may gradually incorporate digital healthcare infrastructure through the promotion of responsible date utilization for research and strategic planning. In that case it might become a model for the advancement of digital healthcare infrastructure that fosters sustainability, equity, and preparedness and at the same time preserving the public trust.
5. Utilize telemedicine and assistive technologies. Japan's healthcare system should build on the progress gained during recent crises by keeping policy changes that made telemedicine easier to use. Utilizing remote monitoring of chronic diseases in remote areas could improve the continuity of medical care and reducing the burden on healthcare facilities. At the same time, the integration of assistive robotics and information and communication technology (ICT) into long-term care systems could make them more efficient, safe, and with higher quality of services. Using these technologies will be very important for making healthcare system more adaptive, accessible and efficient.
6. Promote healthy ageing and prevention. The Japanese healthcare system should focus more on preventive measures that reduce risks before they turn into costly health conditions. Activities of health promotion, preventive measures and systematic screening may delay the onset of disability as well as extend healthy life years, and to reduce future costs (13). Systematic screening should include social determinants of health in primary health care and community-based programs. A strategy that focuses mainly on prevention not only improves individual well-being, but also makes the system more stable in the long run.
7. Improve the integration of mental health care. Adding mental health screening and collaborative care models to primary healthcare may identify timely mental issues and provide prompt treatment. Public campaigns to destigmatize people seeking for medical help just as important as encouraging people to seek medical help without fear or hesitation. Easier access to psychosocial support will help ensure that mental health is seen as an important part of overall health, there promoting equity and sustainability within the system.

Conclusion

The Japanese healthcare system has made remarkable progress, but new challenges will arise in the next decade - an aging population, budget cuts, and rapid technological changes. Solving these problems will require practical reforms. Better integration of health care, more rational use of the workforce, more flexible payment models, and more reliable data processing systems can help ensure universal coverage while increasing equity and sustainability. To move from ideas to results, policies must be tested through pilot projects, formed through collaboration between sectors, and evaluated using clear evidence. With this approach, Japan will be able to continue protecting people's health and well-being while adapting to the realities ahead. Japan's long history of generating new ideas in public health, from its pioneering universal health insurance framework to being known globally for its success in longevity-positions it as a leader in influencing future strategies. If Japan keeps trying out new policies and making evidence-based changes, it will not only sustain its own system but also will be a model for other countries that are dealing with similar demographic and financial issues. In this way, Japan is ready to remain at the top of global public health leadership for many years to come.

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Review Article

Developing and Validating Predictive Models for Adverse Drug Reactions using Electronic Health Records (EHRs): A Narrative Review

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Abstract:

Adverse drug reactions (ADRs) remain a major global challenge, contributing substantially to patient morbidity, mortality, and healthcare costs. Traditional pharmacovigilance approaches—spontaneous reporting and post-marketing surveillance—are hampered by underreporting, delays, and limited contextual data. The growing availability of electronic health records (EHRs), which capture longitudinal structured and unstructured patient information, presents an unprecedented opportunity to advance ADR prediction. This narrative review synthesizes recent progress in developing and validating predictive models that leverage EHRs, highlighting methodological approaches, challenges, and future directions. Predictive strategies range from traditional regression models to advanced machine learning and deep learning architectures, with multimodal frameworks increasingly integrating structured fields (demographics, labs, prescriptions) and unstructured clinical text through natural language processing. While ensemble and deep learning methods demonstrate superior performance, issues of data quality, missingness, bias, and interpretability persist. Robust validation frameworks—spanning internal cross-validation to multi-center external testing—are critical to ensure generalizability and clinical trustworthiness. Ethical considerations, including fairness, privacy, and transparency, remain central to safe deployment. Looking forward, promising avenues include federated learning across institutions, integration of multi-omics and pharmacogenomic data, explainable AI tailored for clinical use, and real-time monitoring through digital twin frameworks. These trajectories, combined with robust governance and clinician–data scientist collaboration, have the potential to transform ADR detection from a reactive process to proactive, personalized prevention. By synthesizing the existing evidence, this review provides insights into the development of more effective predictive models for ADRs and informs strategies for improving pharmacovigilance. This study will contribute to the ongoing efforts to leverage EHRs and predictive models for improving patient outcomes and reducing the burden of ADRs.

Keywords: Adverse Drug Reactions (ADRs); Electronic Health Records (EHRs); Predictive Modeling; Machine Learning; Pharmacovigilance; Artificial Intelligence (AI)

Introduction

Adverse drug reactions (ADRs) is a persistent, challenging and life threatening event encountered in modern medicine which is of public health concern. These unintended, harmful responses to medications—occurring at doses normally used for prophylaxis, diagnosis, or therapy—are a major cause of patient morbidity and mortality worldwide [1]. The spectrum of ADRs ranges from mild discomforts to severe, life-threatening events, and their unpredictability complicates efforts to mitigate risk. Clinical trials and pre-marketing studies often fail to identify the full range of ADRs, leaving clinicians and health systems to depend heavily on post-marketing surveillance, spontaneous reporting systems, and case studies. Yet these traditional methods are hampered by underreporting, delayed detection, and lack of detailed clinical context [1, 2].

The burden of ADRs on patient safety and healthcare systems is substantial. It has been estimated that ADRs account for between 3.6% and 6.5% of hospital admissions [3], with as many as 10-20% of hospitalized patients developing ADRs during their stay [4]; whereas 16% mortality rate was recorded to be associated with ADRs in a cross-sectional survey conducted in South Africa [5]. In older adult populations, the prevalence of ADRs is 11% [6], and it is responsible for 3.3% of hospital admissions, especially amid polypharmacy and multiple comorbid conditions [7]. Beyond patient harm, ADRs impose a significant economic cost on healthcare systems: increased length of stay, extra diagnostic and therapeutic interventions, and in some cases long-term disability. From the perspective of pharmacovigilance, the challenge is heightened by system inefficiencies—including delays in signal detection, incomplete reporting, and limited data on patient-level risk factors.

In recent years, Electronic Health Records (EHRs) have emerged as a promising resource to ameliorate many of these limitations. Data contained in EHRs is broadly categorized into structured data and unstructured data. The structured data include the following information demographics, diagnoses, prescriptions, laboratory results and imaging. On the other hand, the unstructured data include data contained in clinical notes. This category of data provides longitudinal, real-world views of patient health trajectories [1, 8], as well as an opportunity to first hand information relating to drug administration over time, co-morbidities, concomitant drug administration as well as outcomes of therapy (including clinical, patient, economic and humanistic outcomes) [9, 10]. In addition, data from EHRs significantly support research (including both retrospective and prospective studies) and offer opportunities for improved statistical power as well as generalizability as EHR feature large sample size.

Complementing the availability of rich EHR data, predictive modeling using artificial intelligence (AI) and machine learning (ML) has become a dynamic and rapidly expanding strategy to identify patients at risk of ADRs before harm occurs. Machine learning models—such as random forests, gradient boosting, support-vector machines—and more recently, deep learning architectures, knowledge graph embeddings, and attention mechanisms have been applied both to structured EHR data and unstructured clinical text [11, 12]. These approaches have shown promise: for example, AI-based models have achieved high sensitivity and specificity in certain settings, such as oncology or neonatology, and risk scores have been proposed to classify high versus low ADR risk in vulnerable populations [13, 14]. Nonetheless, challenges remain around model validation, transportability, interpretability, and bias.

This narrative review aims to synthesize recent advances in the development and validation of predictive models for ADRs using EHR data. Specifically, our objectives are: (1) to map the landscape of existing ADR-prediction models built from EHRs; (2) to examine the methodologies used for model development—including feature engineering, model selection, and use of structured versus unstructured data; (3) to evaluate how these models have been validated (internal and external), and assess reported performance metrics such as discrimination, calibration, and clinical usefulness; (4) to discuss key challenges (e.g., data quality, missingness, bias, interpretability) and ethical considerations; and (5) to propose future directions and recommendations for research, clinical translation, and governance. By providing this synthesis, we expect this review will help researchers, clinicians, and policymakers to understand what has been achieved, what gaps remain, and how best to leverage EHR-driven predictive modeling in ADR prevention to improve patient safety.

Methodology

PubMed and Google Scholar were the principal sources of literature for this review. Additionally, the reference list of the studied literature was examined to pinpoint more relevant publications. We subsequently examined and integrated findings from the relevant literature thematically in relation to the topic.

Electronic Health Records as a Data Source for ADR Prediction

Electronic Health Records (EHRs) data that captures a patient's journey through healthcare thereby enabling the identification of adverse drug reactions. Hence, such data offer a wide range of opportunities owing to the fact that they provide patient follow-up information across interventions as well as medical and medication records, laboratory investigations and results and pertinent information on responses to various medication classes. This enables not only retrospective studies of ADRs but also potentially near-real-time monitoring. However, EHRs provide valuable insights into real-world clinical practice compared to the controlled environment of clinical trials. Therefore they feature different patient populations as well as multiple comorbidities, polypharmacies that are often underrepresented in trial data. With this real-world features of EHRs medication usage data including drug usage patterns, off-label uses, and rare ADRs may be more visible [14].

Notwithstanding, the adoption of EHRs data for ADR prediction models should be with caution to strengthen data validity and generalizability of findings as EHRs face numerous drawbacks. Amongst such obstacles is "data heterogeneity". This is because different healthcare systems use different coding methods, terminologies, and different EHR platforms. Laboratory test names or units may differ; medication names may be non-standardized; adverse events may be recorded with different vocabularies. Missing data is pervasive: structured fields may be blank, or lab tests may be ordered infrequently; crucial exposures or outcomes may be absent or mis-recorded. Coding errors occur, both in diagnoses and medications: misclassification or undercoding of ADRs is common. Privacy and governance concerns complicate data access and sharing, especially when unstructured clinical notes might contain identifiable or sensitive information.

Within this mixed data environment, Natural Language Processing (NLP) plays a crucial role in extracting ADR signals from unstructured clinical text. Clinical notes often contain descriptions of symptoms, side effects, drug tolerability, temporal relationships (e.g., when a reaction started relative to drug administration), and free-text contextual details that structured fields miss [15]. Recent work has shown that integrating structured and unstructured data via NLP can significantly increase sensitivity in detecting ADRs. For example, pediatric pharmacovigilance studies demonstrate that many adverse drug events are recorded only in clinical notes but not in diagnostic codes or billing data. NLP pipelines, including rule-based methods, traditional supervised learning models, and more recently transformer-based architectures, have been applied to identify drug-reaction pairs, to extract medication information from narrative text, and to normalize these into standard terminologies (e.g., RxNorm, MedXN) [16]. Tools that adopt interoperability standards, such as Health Level Seven Fast Healthcare Interoperability Resources (HL7 FHIR), to encode extracted substance, timing, and reaction attributes help ensure that output features are usable across institutions [17].

Overall, Figure 1 provides suitable illustration of how EHR data flows from raw form to a state usable for predictive modeling. First, multiple raw EHR sources provide structured data (demographics, prescriptions, labs, diagnoses, etc.) and unstructured data (clinical notes, narratives). This raw data must undergo cleaning and preprocessing: dealing with missing data, standardizing codes, normalizing units, detecting and removing duplicates or errors, ensuring privacy via de-identification. After cleaning, feature engineering constructs predictors from the data: drug exposure histories (dose, duration), patient covariates (comorbidities, age, sex, lab trends), temporal relationships, perhaps signal features derived from text (frequency of symptom mentions, co-occurrence). Then the modeling stage applies machine learning or deep learning methods, perhaps including multimodal models that combine structured and text-derived features. Finally, model outputs include risk prediction (probability of an ADR), risk stratification (low, moderate, high risk), and alerts or decision support suggestions. The pipeline ensures that the expressive content of EHRs is converted into usable features while maintaining validity, transparency, and reproducibility.

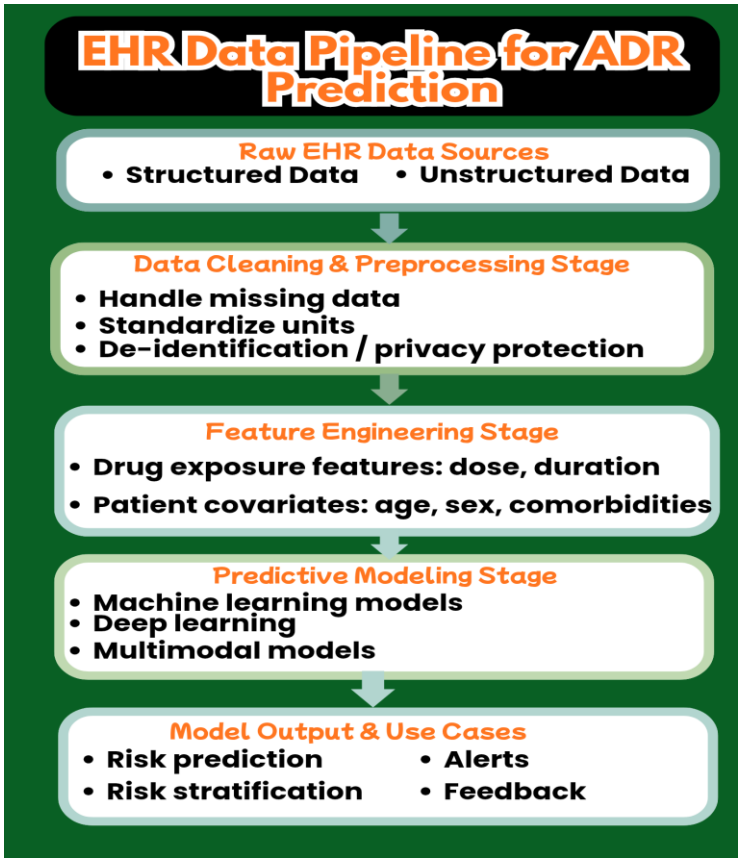
EHR Data Pipeline for ADR Prediction
Raw EHR Data Sources
• Structured Data • Unstructured Data
Data Cleaning & Preprocessing Stage
• Handle missing data
• Standardize units
• De-identification / privacy protection
Feature Engineering Stage
• Drug exposure features: dose, duration
• Patient covariates: age, sex, comorbidities
Predictive Modeling Stage
• Machine learning models
• Deep learning
• Multimodal models
Model Output & Use Cases
• Risk prediction • Alerts
• Risk stratification • Feedback

Figure 1: Pipeline for ADR Prediction Using EHRs Data

Predictive Modeling Approaches for ADRs

There are many approaches that have been found to be useful in the growing field of ADR prediction. Such as statistical modeling, machine learning, and deep learning approaches. Each is associated with different assumptions, strengths, and limitations. Whereas classical statistical modeling provides interpretability and simplicity, modern machine learning and deep networks seek to capture nonlinearities, interactions, and high-dimensional signals; hybrid models aim to harness both structured and unstructured data to optimize performance. We discussed these approaches in detail under the following headings:

Traditional Statistical Methods

These are the oldest mathematical models that have been found useful in biomedical prediction. They include logistic regression and Cox proportional hazards modeling and they have been the starting points in ADR research. For example, in logistic regression, the log-odds of an ADR event as a linear function of covariates (drug exposures, patient comorbidities, demographics) is modeled. Its appeal lies in interpretability: estimated coefficients can be directly understood as odds ratios, facilitating clinical insight. Cox proportional hazards models extend this to time-to-event frameworks, modeling the hazard of ADR occurrence as a function of covariates over follow-up time, accommodating censoring of patients who never experience the ADR.

Although these models have recorded great success in their application, they are faced with a lot of limitations in their application in ADR prediction. Usually they often assume linear effects (in logistic regression), proportional hazards (in Cox models), and require prior specification of interaction terms. In high-dimensional settings—such as when combining labs, medication histories, and text-derived features—the curse of dimensionality and multicollinearity may hinder performance. Furthermore, complex, nonlinear interactions or latent factors in EHRs may be missed. That said, logistic regression is still often used as a baseline or benchmark in comparative modeling studies [18, 19].

Machine Learning Techniques

To overcome the linearity constraints of traditional models, machine learning (ML) techniques have been widely adopted in ADR prediction. Core methods include decision forest and tree-based ensembles (e.g. random forests, gradient boosting machines), support vector machines (SVMs), and other kernel methods. These models are capable of capturing nonlinear relationships and interactions implicitly, and can usually

handle higher-dimensional feature spaces as long as overfitting is managed.

In a notable work, Hu et al. (2024) [19] systematically reviewed ADR prediction using machine learning and noted that ensemble models such as random forests, XGBoost, and AdaBoost often outperform simpler classifiers under appropriate regularization and tuning. Zhao et al. (2021) [20] applied a variety of ML methods (SVM, random forest, AdaBoost, XGBoost) on an imbalanced EHR-derived ADR dataset, combining structured and text features, and found that ensemble methods improved predictive performance and robustness compared to traditional logistic regression. Additionally, they utilized ensembling in order to reduce the effects of class imbalance, which is a persistent problem when the number of adverse drug reaction (ADR) occurrences is small in comparison to the number of non-events.

The adoption of gradient boosting, particularly XGBoost and LightGBM, has become a popular method for biomedical predictive tasks. This is because it constructs additive models by sequentially focusing on residuals, which enables excellent performance and the ability to handle missingness. The black-box aspect of support vector machines (SVMs), as well as the complexity of parameter adjustment, sometimes hinders interpretability and clinical acceptance. However, the potential of SVMs to work in high-dimensional feature spaces utilizing kernel tricks has led to their employment in adverse drug reaction (ADR) scenarios.

Overall, these models—even those that employ strong machine learning methods—generally necessitate meticulous feature building, as well as risk of overfitting, and may not exhibit internal transparency. Thus, many recent efforts have turned to deep learning to further push the frontier.

Deep Learning Approaches

Deep learning (DL) architectures are well-suited to capture complex hierarchical and latent patterns in large-scale data. In the ADR domain, neural networks—including feedforward deep neural networks, recurrent neural networks (RNNs), and transformer architectures—have been used to integrate heterogeneous features, model longitudinal trajectories, and process unstructured text.

Moreover, Mohsen et al. (2010) [21] combined drug-induced gene expression profiles from the Open TG-GATEs database with FAERS ADR labels to train deep neural networks for ADR prediction, achieving mean classification accuracy of 85.7% across modeled endpoints. This illustrates the power of DL in integrating multi-omics signals with pharmacovigilance data. In other work, convolutional neural networks have also been applied to encode drug and ADR embeddings for prediction in combination therapies [22].

RNNs, including long short-term memory (LSTM) networks, are particularly advantageous in modeling longitudinal EHR sequences—capturing temporal dependencies in lab values, drug changes, and patient state. Transformer architectures, recently adapted for healthcare timeseries and clinical text, offer even greater capacity for modeling long-range dependencies and attention-based weighting of features.

One recent model, ADRNet, presents a hybrid collaborative-filtering + representation-learning architecture that integrates both clinical ADR occurrence data and non-clinical drug descriptors (e.g. chemical, biological features). ADRNet uses a shallow collaborative filtering module to capture co-occurrence patterns and a deep drug representation network to guide latent embeddings, thus bridging structured and unstructured (descriptor) domains [23].

Graph neural networks (GNNs) have also gained traction. Kwak et al. (2020) [24]constructed a drug-disease graph from claims/EHR disease codes and applied GNNs to learn node embeddings predictive of drug-ADR associations; their model achieved AUROC ~0.795, demonstrating the power of relational learning.

Hybrid / Multimodal Models (Structured + Unstructured Data)

To exploit the full richness of EHRs, hybrid models that fuse structured features (labs, diagnoses, medications) and unstructured text features (symptom mentions, narrative context) have emerged. It is typical to use a two-branch architecture: one branch is an ML or DL pipeline for structured inputs, and the other is an NLP encoder (for example, BERT or CNN) for text, with fusion layers integrating latent representations later on. This enables the model to take use of both numerical precision and subtleties included in the actual narrative.

For instance, it is frequently discovered that research that employs a combination of structured and narrative features lead to improvements in sensitivity or positive predictive value when compared to structured-only models. The added information provided by clinical notes is especially useful in resolving ambiguous signals, determining the timing of adverse events, and distinguishing between incidental symptoms and those that are related to the medicine in question.

One example of a deep representation model that utilizes multimodal longitudinal EHRs is Patient2Vec. Although its major focus was on predicting hospitalizations rather than adverse drug reactions, its architecture

provides an illustration of how mixed temporal EHR data can be used to develop interpretable embeddings. Its attention mechanism allows one to gain an understanding of which visits or features have an impact on predictions. It is possible to make adjustments to alternative dispute resolution (ADR) models by using comparable design concepts [25].

Synthesis and Lessons Learned

From the diverse landscape of ADR prediction modeling, several key patterns emerge. First, there is no one-size-fits-all algorithm: logistic regression may suffice as a baseline, but more flexible ML and DL models are often required to capture EHR complexity. Second, as model complexity increases, so does the importance of rigorous validation, regularization, and interpretability methods (e.g. feature importance, attention weights). Third, hybrid and multimodal models that bring together structured, unstructured, and external drug knowledge (via embeddings or graphs) consistently show promise for improved discriminative ability. Finally, limitations in data quality, class imbalance, and generalizability remain major challenges across studies, which must be carefully addressed in any implementation or translation to clinical practice.

Model Validation and Evaluation Frameworks

In predictive modeling for adverse drug reactions (ADRs) using EHRs, building a model is only half the battle. Without rigorous validation, even a model with seemingly excellent performance in development can collapse under new data, overfit to quirks of the development set, or produce biased estimates when transported to other settings. Robust validation guards against overfitting, quantifies how well the model generalizes, and helps ensure that risk predictions remain dependable when deployed in real clinical environments [26, 27]. Indeed, the dictum "there is no such thing as a validated model" (i.e., models must continuously be tested and updated) underscores that validation is never a one-time check but a continuous scrutiny of performance across settings and time [28].

A central distinction in validation strategies lies between internal and external validation. Internal validation evaluates model performance using the same dataset (or subsets thereof) on which the model was developed, typically via cross-validation (e.g., k-fold), bootstrapping, or split-sample approaches. The aim is to correct for optimism—i.e., the tendency of a model to appear overly strong on training data due to overfitting [27, 29]. Bootstrapping is often preferred because it makes efficient use of all data and provides optimism-corrected estimates of performance. In contrast, cross-validation (e.g. 5- or 10-fold) partitions the data to iteratively test "held-out" folds, giving an estimate of reproducibility. Temporal cross-validation (e.g. training on earlier time periods, testing on later ones) is especially relevant in EHR-based studies, where data drift over time is common.

Yet internal validation alone is insufficient when the ultimate goal is deploying a model in novel settings. External validation assesses model performance in datasets entirely independent from the development cohort—whether from a different hospital, geographic region, or time period (temporal validation). Its purpose is to evaluate transportability and generalizability [30]. Good external performance suggests that the model has captured more fundamental patterns rather than idiosyncrasies of a particular site. However, as Van Calster et al. (2023) [28] and la Roi-Teeuw et al. (2024) [31] caution, an external validation in a single new dataset is never proof of universal validity; models must be assessed across multiple contexts, and calibration drift over time must be monitored. Misconceptions about external validation—treating it as a singular "seal of approval"—remain widespread [31].

When assessing model performance, several metrics become key. Discrimination—the ability to distinguish patients who will develop an ADR from those who will not—is commonly quantified by the Area Under the Receiver Operating Characteristic (AUC or c-statistic). In time-to-event settings, concordance (C-index) may serve a similar role. However, good discrimination alone is insufficient. Calibration, which measures how closely predicted probabilities align with observed event frequencies, is often called the Achilles' heel of predictive models [32]. Calibration assessment includes calibration-in-the-large (systematic over- or under-prediction), calibration slope (overfitting/underfitting), and graphical calibration plots. A model with excellent discrimination but poor calibration may mislead clinicians if its probabilities are untrustworthy. Complementing discrimination and calibration, assessing clinical utility is essential: decision curve analysis, net benefit, and threshold analysis show whether a model's predictions would lead to better decision-making or patient outcomes rather than mere statistical performance [32].

Yet even with internal and external validation and a full set of metrics, the challenge of generalizability and transportability across health systems remains formidable. Differences in patient populations, case mix, measurement protocols, medication formularies, and

practice patterns can degrade performance in new settings. For example, if one hospital uses a different laboratory analyzer that shifts reference ranges, or prescribes different drug brands, predictor distributions might shift, inducing calibration drift or reduced discrimination [33]. In addition, heterogeneity in patient features or coding practices may exacerbate these issues [34]. Further, as newer interventions, changing disease prevalence, or updated protocols emerge, the model's relationships may become outdated, requiring recalibration or retraining.

A number of techniques have been suggested in order to address these difficulties. The ability of the model to generalize across centers can be evaluated through the use of internal-external cross-validation, which involves splitting by centers or clusters and leaving one center out in each fold. According to Riley et al. (2016) [35], meta-analyses of performance across external validations can provide a quantitative measure of heterogeneity. It is essential to sustain performance as practice advances by continuously monitoring and updating dynamic models, periodically recalibrating them, and employing model updating strategies [36]. Furthermore, the idea of targeted validation emphasizes the importance of validating in the population and setting where the model is expected to be utilized as opposed to verifying in arbitrary external cohorts [29]. In addition, the validation settings, participant selection, and overall performance heterogeneity need to be reported with complete transparency, such as through TRIPOD [26].

Key Challenges and Ethical Considerations

The development and deployment of ADR predictive models using EHRs, faces significant challenges. These problems are not only technological problems, they also relate to ethical issues and are discussed in the subsequent paragraphs. However Table 1 offers actionable insights that can be followed to address these challenges.

Amongst these problems are those pertaining to EHR data quality and missing data. Clinical systems were not designed for research, therefore data gaps, errors, and inconsistent recording are common. Opportunistic laboratory tests and vital signs may be recorded, and many patients may overlook critical factors. Algorithms struggle with numerical features with high missing fractions because imputation may introduce bias or variance [37]. A recent study of missing data management in EHRs indicated that while machine learning–based imputation algorithms including multiple imputation, KNN, and matrix factorization show promise, no single approach prevails across use scenarios [38]. Coding errors—mislabeling diagnoses, drug entries, or adverse events—are widespread and degrade model signals. Poor data quality can thus propagate to flawed predictions or overconfident models.

Closely intertwined is the issue of algorithmic bias and disparities in prediction across demographic groups. Because EHR data reflect historical care patterns—often marred by existing health inequities—models trained on them may reproduce or even magnify bias [39, 40]. A canonical example outside ADR modeling is the algorithm used for risk prediction in health systems, which assigned lower risk scores to Black patients with equivalent needs, leading to less access to care [41]. In the ADR context, this could mean that minority populations or underserved groups may systematically receive underpredicted risk, thereby undermining equity in clinical decision support. Reviews of bias in EHR-based AI emphasize multiple bias types—selection bias, measurement bias, confounding bias, temporal bias—and the need for structured mitigation strategies [42, 43]. Unless addressed, algorithmic bias can compromise both fairness and the ethical legitimacy of predictive models.

Turning to governance, data privacy, governance, and the ethics of secondary EHR use must be carefully negotiated. Clinical narratives, even when de-identified, may carry re-identification risks, especially when combined across variables or with external data sources. Legislation such as GDPR in Europe, and evolving biomedical data policies, emphasize the need for transparency, consent, minimal data use, and accountability in algorithmic deployment. Scholars argue that algorithmic ethics must be proactive, not an afterthought: embedding algorithmic audits, human-in-the-loop review, and dynamic compliance monitoring increases trust [44]. In contexts with weaker data protections, secondary use of EHRs can raise concerns of exploitation, patient autonomy, and community consent—particularly when certain populations are overrepresented in datasets.

Even if one overcomes data and governance challenges, interpretability and explainability of ML and deep learning models remain a central ethical and practical hurdle. Clinicians and patients may resist a "black box" recommendation whose logic cannot be scrutinized. Interpretable machine learning (IML) methods—such as attention mechanisms, feature importance, rule extraction, surrogate models—attempt to bridge this

gap. Yet many methods struggle in balancing fidelity (how closely explanations reflect true model logic) with simplicity (how understandable they are) [45]. The healthcare domain demands trust: systems like RETAIN illustrate how reverse-time attention models can yield predictions while preserving interpretability [46]. Tools such as VBridge have also been proposed to visually connect explanatory features to patient records to help clinicians interpret model decisions [42]. Nonetheless, poor or misleading explanations may lead to distrust, misunderstanding, or misuse.

Finally, even assuming model performance and interpretability are adequate, regulatory and clinical acceptance barriers can stymie adoption. Clinicians may fear accountability for following or rejecting algorithmic advice, especially if the model is unclear. Institutional governance, medical device regulation, and approval processes vary by jurisdiction, and many regulatory frameworks are not yet ready for clinical predictive algorithmic technologies. Unless AI models prove their value and explainability, physicians may favour simpler decision criteria or conventional risk scores. The "last mile" of implementation—integrating forecasts into clinical workflows, aligning incentives, retraining staff, and monitoring—is sometimes harder than model training.

Table 2: Challenges Associated with Developing and Deploying ADR Prediction Models using EHRs

Challenge	Description	Example	Potential Mitigation Strategy
Incomplete data entry	High proportions of missing entries or variable absence	Lab test values missing in many patient records	Use robust imputation (multiple imputation, ML methods), auxiliary data, or missingness modeling
Coding errors	Misclassification of diagnoses, drugs, adverse events	ADR event coded incorrectly or omitted in ICD codes	Cross-validation against narrative notes, audit samples, NLP to detect contradictions
Population bias / disparities	Training data unrepresentative of minority or marginalized groups, leading to skewed performance	Underprediction in racial minorities	Stratified modeling, fairness-aware training, oversampling or reweighting, bias audits
Data privacy & governance	Risks to patient confidentiality and consent in secondary EHR use	Re-identification risk from combinations of variables	De-identification, federated learning, differential privacy, ethics review, transparency policies
Interpretability / explainability	Black box models whose decisions are opaque to clinicians	Deep NN giving ADR risk probability without insight	Use inherently interpretable architectures, post-hoc explanation methods, attention-based models
Clinical integration / acceptance	Resistance or logistical barriers to embedding models into practice	Clinicians ignoring alerts or refusing to trust AI output	Engage end-users early, iterative usability design, clinician–AI collaboration frameworks, education

Clinical and Research Implications

The implementation of prediction models for adverse drug reactions (ADRs) is expected to have a significant impact on the fields of pharmacovigilance, clinical decision support, personalized medicine, and the life cycle of drug development. If such models are carefully deployed and validated, they have the potential to transform the current paradigm of reactive detection of ADRs into proactive prevention, thereby improving patient safety, decreasing the burden on healthcare systems, and catalyzing innovation in the field of drug safety research.

Pharmacovigilance systems can be greatly improved by predictive ADR models. Spontaneous reporting, human case review, and statistical signal detection can lag behind real-world events in traditional pharmacovigilance. Using predictive models in surveillance pipelines can speed up ADR identification, prioritize high-risk drug–patient combinations for further assessment, and filter false positives by ranking likely true signals [47, 48]. Using real-world data, a preliminary predictive surveillance model identified product safety signals [49]. By continuously scanning EHRs, claims, and integrated sources, ADR prediction systems may catch safety signals earlier than traditional methods, thus reducing patient harm and informing regulators more swiftly.

Second, the integration of predictive models into clinical decision support systems (CDSS) is a critical path to translation. Embedding ADR risk scores or alerts into the electronic prescribing workflow can help clinicians anticipate and avoid harmful drug–patient interactions before they occur. However, to be accepted, these alerts must be clinically credible, actionable, and minimally disruptive to workflow. Models should provide not only a risk probability but also contextual justification (e.g., contributing risk factors) to support clinician understanding and trust. Furthermore, continuous feedback loops—where clinician responses feed back into model refinement—can help maintain performance in real practice settings [50].

Beyond prevention of harm, ADR prediction models can enhance personalized medicine and risk stratification. Because patients differ in genetics, comorbidities, drug metabolism, and polypharmacy, a one-size-fits-all approach to drug safety is often inadequate. Predictive models trained on large, heterogeneous EHR datasets can uncover individualized risk profiles, enabling tailored prescribing (e.g., selecting safer alternatives, adjusting doses, monitoring more intensively) for patients at high predicted risk. In this way, ADR prediction becomes a component of precision therapeutics, aligning safety measures with individual vulnerability.

Moreover, ADR prediction models have an important role across the drug development and post-marketing surveillance continuum. During drug development, models trained on preclinical, mechanistic, and early-phase human data may help anticipate safety liabilities before large trials. For instance, deep learning models combining gene expression and toxicity data have shown promise in flagging potential adverse outcomes early [21]. In post-marketing surveillance, predictive models may complement spontaneous reporting by continuously reassessing risk as new real-world data accumulate, and by identifying patient subgroups at disproportionate risk. In regulatory contexts, predictive models may support adaptive safety monitoring, dynamic labeling, or conditional risk mitigation plans.

On the other hand, these aspirations related to translation necessitate meticulous coordination. Model performance needs to be consistent across different environments, interpretability needs to meet the requirements of physicians and regulators, governance frameworks need to protect patient privacy and responsibility, and deployment needs to conform to existing clinical infrastructure. As a matter of fact, the most significant obstacles frequently encountered in practice do not originate in the building of the model but in the processes of integration, trust, maintenance, and ongoing validation.

Future Directions in ADR Prediction Research

As the concept of ADR prediction grows, the frontier is moving towards systems that are scalable, privacy-aware, multimodal, and interpretable systems that can be implemented across institutions and feature deeper biological insights. There are a number of new trajectories that show a great deal of potential and merit consideration.

Multi-center and federated learning for ADR modelling is one of the promising breakthroughs. Hospitals and health systems routinely silo adverse event data, reducing sample diversity and generalizability. Federated learning facilitates model training across sites without exchanging patient-level data, protecting privacy while learning from more populations [51]. A federated approach that pooled local models to generate a global ADR predictor by Choudhury et al. (2020)

[52] showed that decentralized learning is possible without losing data sovereignty. Recently, Guo and Choo (2025) [51] examined how federated learning and large language models might improve ADR prediction across institutional borders, particularly for unstructured clinical material. Nevertheless, federated learning in healthcare still faces thorny challenges—statistical heterogeneity (non-IID data), communication overhead, model aggregation strategies, and privacy attacks [53]. Advances in meta-learning federated frameworks (e.g., FedMetaMed) may help models better adapt to local idiosyncrasies while benefiting from shared knowledge [54].

Beyond distributed training, another rich frontier is the integration of genomics, pharmacogenomics, and multi-omics data with EHR-derived features. ADR susceptibility is often mediated by variation in drug metabolism genes, transporters, or molecular pathways; thus, combining molecular-level data with clinical trajectories can refine risk models. Recent reviews in pharmacogenomics highlight that AI and multi-omics integration can improve precision in predicting drug toxicity across contexts [55]. The fusion of longitudinal EHR time series with genotype or expression data could capture the interplay of patient biology and therapy exposure. In cancer pharmacovigilance and cardiology, hybrid models that blend omics and clinical features have begun to show incremental gains over clinical-only predictors. As sequencing becomes more routine, this direction will only strengthen.

Closely tied is the drive to design explainable AI (XAI) techniques tailored for clinical ADR prediction and adoption. While powerful predictive models are already feasible, their opaque nature poses a barrier to use. Recent surveys of XAI in medical settings emphasize that methods such as SHAP, LIME, counterfactual explanations, and attention visualization have promise but often falter in clinical fidelity and interpretability tradeoffs [56, 57]. The challenge is to tie explanations back to domain concepts—drug mechanisms, temporal relationships, lab trends—so clinicians can verify or contest predictions meaningfully. Emerging hybrid strategies that embed mechanistic knowledge or causal constraints, or that extract human-interpretable rules from deep models, may help bridge this gap. Systematic benchmarks of XAI methods in real-world ADR datasets remain scant; thus, future work should compare interpretability techniques under realistic clinical settings, not just synthetic tasks.

Another exciting horizon lies in digital twins, real-time ADR monitoring, and global EHR collaborations. The notion of a medical digital twin—a continuously updated in silico replica of a patient's physiological and therapeutic state—offers a paradigm in which ADR risk is simulated and forecast before it emerges [58]. In such frameworks, the twin may ingest EHR changes, wearable signals, pharmacokinetic/pharmacodynamic models, and molecular inputs to predict future events in silico. The twin could be used to "stress test" alternate drug regimens and flag high-risk trajectories. In practice, early efforts are underway in cardiology and metabolic disease, though ADR-specific instantiations remain nascent [59]. Closely allied is the idea of real-time ADR monitoring, where streaming EHR data or device inputs feed prediction engines to detect adverse signals as they unfold, triggering alerts or adaptive monitoring. At a broader scale, global EHR collaborations (e.g., federations of health systems sharing model weights or summary statistics) can amplify population diversity, improve external validity, and support comparative safety meta-analyses.

Given these trajectories, we propose several recommendations for the research and policy community. First, researchers should prioritize multi-site, prospective validation studies: models should be tested in live EHR settings across geographies and care systems to assess robustness and drift. Second, standardized reporting frameworks—extending TRIPOD to cover federated, multimodal, and XAI models—should be adopted, ensuring transparency of data provenance, fairness audits, and explanation methodology. Third, funding agencies and institutional review boards should support privacy-preserving data enclaves, federated infrastructure, and collaborative networks, especially in low-resource settings. Fourth, policy makers and regulators must evolve frameworks for algorithmic safety, liability, and continuous post-deployment monitoring; regulatory paradigms should treat ADR prediction models as evolving medical devices requiring lifecycle oversight. Finally, bridging the academic–clinical interface is crucial: clinicians, pharmacologists, data scientists, and informaticians should co-design models, evaluation protocols, and interpretability interfaces so that algorithmic insights are actionable, trustworthy, and aligned with workflow.

In sum, the future of ADR prediction is not simply more complex models, but smarter architectures—privacy-aware, interpretable, biologically informed, and globally generalizable. The confluence of federated learning, multi-omics integration, explainable AI, digital twin architectures, and real-time monitoring offers a roadmap to transform predictive pharmacovigilance from a hopeful concept into a standard of clinical safety.

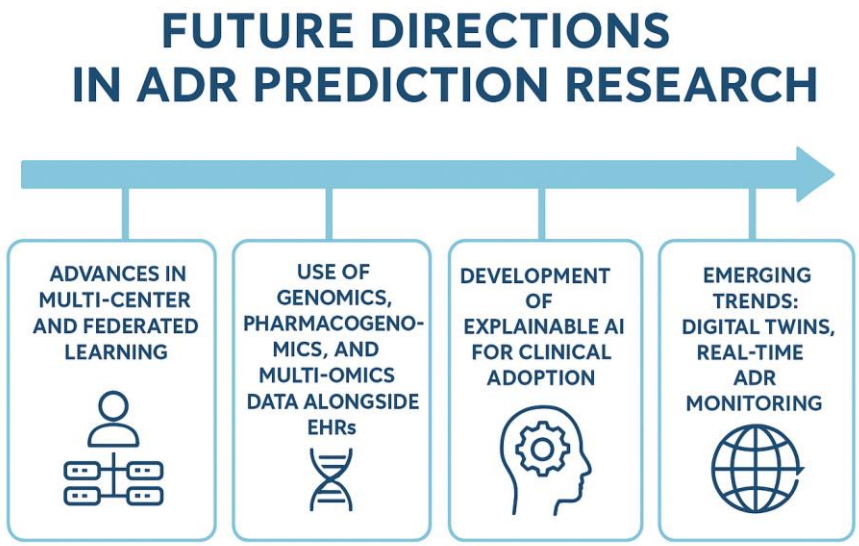
FUTURE DIRECTIONS
IN ADR PREDICTION RESEARCH
ADVANCES IN MULTI-CENTER AND FEDERATED LEARNING
USE OF GENOMICS, PHARMACOGENO-MICS, AND MULTI-OMICS DATA ALONGSIDE EHRs
DEVELOPMENT OF EXPLAINABLE AI FOR CLINICAL ADOPTION
EMERGING TRENDS: DIGITAL TWINS, REAL-TIME ADR MONITORING

Figure 3: Future Research Roadmap for ADR Prediction Models

Conclusion

This review demonstrates that predictive modeling using electronic health records is redefining how adverse drug reactions are identified and prevented. By leveraging machine learning, deep learning, and multimodal integration, these models promise earlier detection and improved patient safety compared to traditional pharmacovigilance methods, which are hindered by underreporting and delayed signal capture. However, their potential is constrained by challenges of data quality, algorithmic bias, interpretability, and limited clinical uptake. Robust validation—across internal, external, and multi-center settings—remains essential to ensure models are reliable and generalizable in real-world use. Looking ahead, advances such as federated learning, multi-omics integration, explainable AI, and digital twin frameworks present transformative opportunities. Yet, progress must be accompanied by strong governance, transparency, and interdisciplinary collaboration. For clinicians, researchers, and policymakers alike, the path forward lies in co-designing systems that are technically sound, ethically responsible, and clinically meaningful. If achieved, predictive ADR models can evolve from experimental tools into trusted components of modern pharmacovigilance and personalized medicine.

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Review Article

Antiepileptic Drugs and Parkinson's Disease: A Meta-Analysis of Existing Evidence

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Abstract:

Background. There is growing interest in the association between antiepileptic drugs (AEDs) exposure and subsequent Parkinson's disease (PD).

Methods. We conducted a literature search in the PubMed, SCOPUS, and Web of Science databases. We identified studies using an observational design and performed a meta-analysis to evaluate the association between AEDs exposure and incident PD. We assessed the quality of the studies and identified the pooled odds ratio (OR) for those exposed to AEDs compared to those who were not.

Results. Of the 1,775 unique studies identified, 55 were selected for full-text review. Five studies (n = 127,324) were included. Quality assessment revealed moderate-to-high methodological quality in the studies included. The overall OR for a PD was 1.82 (95% CI: 1.35-2.45) in AEDs recipients. When considering each drug individually, the magnitude of association was highest for valproate (OR 3.94, 95% CI: 3.15-4.92) and lowest for carbamazepine (OR 1.32, 95% CI: 1.16-1.49). Further interaction tests revealed higher odds for lamotrigine than for carbamazepine and valproate than for carbamazepine and lamotrigine.

Conclusion. This study revealed potential associations between AEDs and incident PD. However, existing evidence remains insufficient, making it premature to draw inferences on this matter.

Keywords: Antiepileptic Drugs; AEDs; Antiseizure Medications; Epilepsy; Parkinson's Disease

Introduction

Neurological disorders represent an area of particular interest, given their pronounced contribution to global disability estimates (1, 2). Epilepsy and Parkinson's disease (PD) are among the most prevalent chronic conditions and are both associated with an increased disability burden worldwide (3). Despite advances in treatment and a better understanding of disease progression, the exact pathophysiological mechanisms remain unclear (4, 5).

Despite the lack of a genetic correlation between epilepsy and PD (6), the existing literature suggests a bidirectional association (7) and possible shared mechanisms (8). Recent studies have revealed a temporal relationship between these conditions (9, 10); however, it is challenging to explore the contribution of antiepileptic drugs (AEDs) to PD due to insufficient data on medication history. Although AEDs are mostly used for seizure treatment, their prescriptions frequently go beyond this (11). Hence, AEDs may account for some association between epilepsy and PD, highlighting the need for further research.

Studies on PD risk factors have become an important research topic over the last few decades. Despite existing evidence on the temporal relationship between epilepsy and PD, it remains unclear whether epilepsy or its treatment contributes to an elevated risk of PD. Thus, the relationship between AEDs exposure and subsequent diagnosis of PD is of growing interest. Currently, there is an increasing number of observational studies in this field that lack critical summaries. Recognizing the rising interest and existing literature gap, we conducted a meta-analysis to evaluate the association between AEDs exposure and incident PD.

Methods

Overview and outcome measure

This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (12) and was registered with PROSPERO (CRD42024603543). This analysis focused on studies conducted in diverse clinical settings and geographical locations, involving patients taking AEDs for various conditions and not limited to epilepsy. The outcome of interest was incident PD-specific symptom episodes confirmed through hospital episode statistics in patients exposed to AEDs compared to those who were not taking AEDs. This association was expressed as odds ratios (OR).

Literature search

Two reviewers (RA and DK) examined the titles, abstracts, and full texts of all potentially eligible publications with the assistance of a third reviewer (RK) using broad criteria to allow the inclusion of any potentially relevant study for further evaluation. The authors conducted a comprehensive literature search in three bibliographic databases: PubMed (1953–2024), Scopus (1987–2024), and Web of Science (1993–2024) on October 23, 2024, using combinations of the terms "antiseizure drugs," "antiepileptic drugs," "parkinsonism," and "Parkinson's disease," without restrictions on language or publication date. Eligible studies included original research examining the association between AEDs exposure and parkinsonism or PD. Full details of the search strategy are provided in the Appendix (Supplemental Table 1). Additionally, we manually searched the reference lists of the included papers and individually identified articles on the topic to identify additional eligible studies.

Table 1. Characteristics of included studies.

Authors (year)	Study type	Study entry period	Sample size (total)	Data source	Country	Age range at study entry	AED prescription diagnoses (ICD codes)	Outcome	Confounders
Hwang et al., (2024)	Matched cohort study	2002-2013	10,510	National Health Insurance	South Korea	Between the ages	Epilepsy (G40), status epilepticus (G41), Landau-	PD	Age, Sex, economic status, residential area, body Mass

(13)				Service Health Screening Cohort		of 40 and 79 years	Kleffner syndrome (F803), convulsion (R56)		Index, smoking, drinking, hypertension, type 2 diabetes mellitus, ischemic heart disease, congestive heart failure, traumatic brain injury, central nervous system
Belete et al. (2023) (14)	Nested case-control study	1990 - 2008	10,031	UK Biobank	UK	Between the ages of 40 and 69 years	NA	PD	Epilepsy, race and ethnicity
Kostev et al. (2023) (15)	Matched case-control study	2010-2021	49,900	IQVIA Disease Analyzer database	Germany	≥18 years	Epilepsy (G40), restless legs syndrome (G25.8), diabetic/toxic/drug-induced neuropathy (G62, E10.4, E11.4, E14.4)	PD	NA
Zhang et al. (2023) (16)	Nested case-control study	NA	6,174	Electronic health primary care records in East London	UK	NA	NA	PD	Age, sex, ethnicity, index of multiple deprivation, and epilepsy diagnosis
Skow et al. (2013) (17)	Matched case-control study	1990-2008	50,709	UK General Practice Research Database	UK	NA	NA	PD	Body mass index, smoking status, alcohol consumption, use of calcium channel blockers, annual consultation rate

Selection of studies

Full-text articles were assessed for inclusion by two reviewers (RA and DK). Studies were included if they involved patients exposed to AEDs, reported the occurrence of PD, or presented PD-associated symptoms confirmed by clinical assessment, medical records, or databases with a stated diagnosis following AEDs exposure. Articles were excluded if they met any of the following criteria: no reports on PD, case series, case reports, brief reports, editorials, letters, reviews, studies lacking clear reporting on the outcome of interest, studies not specifically reporting on exposure, and studies performed in animals. Detailed information on the excluded studies is provided in the Appendix (Supplemental Table 2). The quality of the studies was assessed using the Newcastle-Ottawa Scale (NOS). All studies

were independently rated by DK and DA and checked by RK to resolve any disagreements.

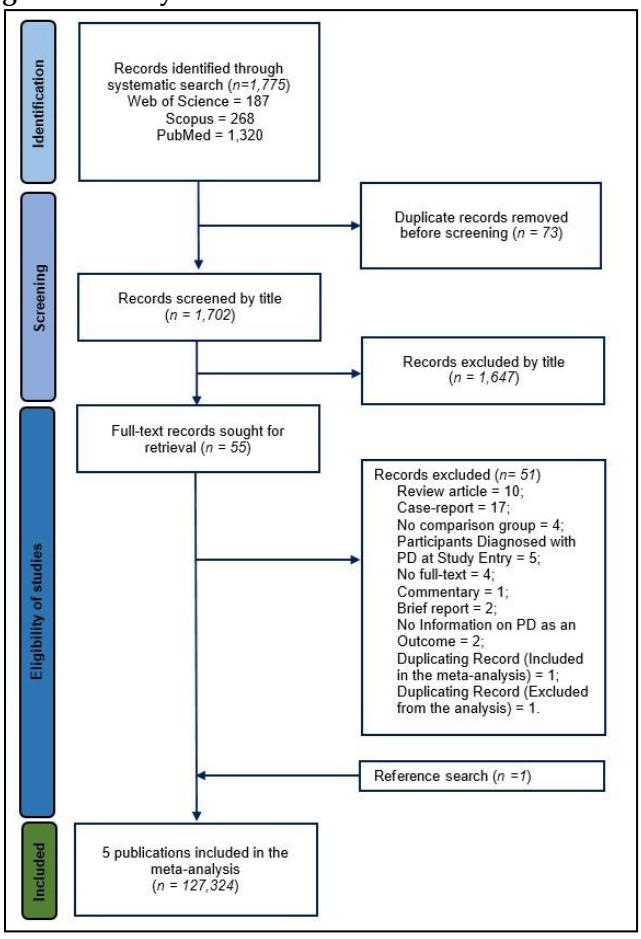
Statistical analysis

We developed a standardized data extraction form using Microsoft Office software. For the full-text publications included, two reviewers (RA and DK) separately retrieved and cross-checked the data, including research details, participant characteristics, and data required to compute pooled ORs. Furthermore, we extracted data on incident PD and stratified them according to AEDs type (if such data were available). A meta-analysis was performed using random-effects models, and 95% confidence intervals (95% CIs) were reported. We calculated heterogeneity estimates for the pooled estimates using the I^2 statistic and determined their significance using the Cochran's Q test p-value. We provided funnel plots, and their asymmetry was examined using Egger's regression tests to identify small study biases. To account for the family wise error, we incorporated a Bonferroni correction for multiple comparisons as α/n, where α and n are the significance level and the number of comparisons conducted within a specific (subgroup) meta-analysis, respectively. All statistical analyses were performed using STATA (V18).

Results

The literature search identified 1,775 studies. After eliminating duplicates, we examined 1,702 distinct citations to determine their eligibility criteria. Of these, 55 abstracts and full-text publications were examined, and five distinct studies (13-17) were found to be suitable for the meta-analysis (Figure 1).

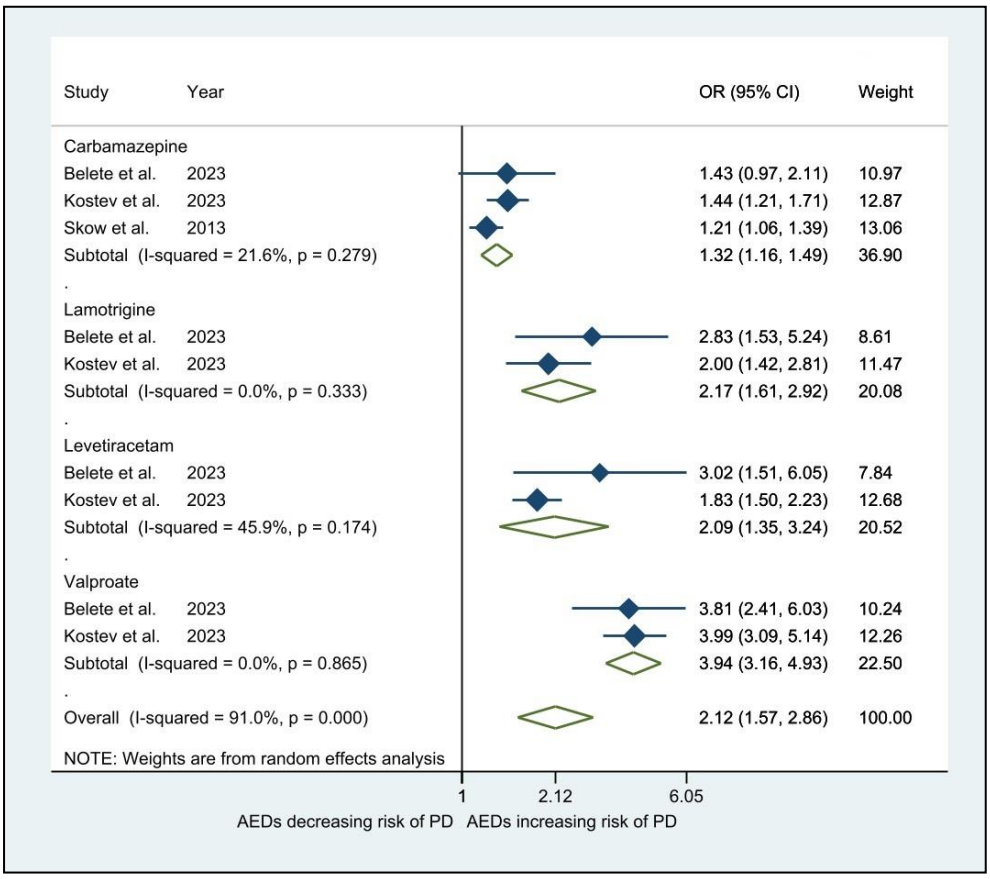
Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of the systematic search.


Identification
Screening
Eligibility of studies
Included
Records identified through systematic search (n=1,775)
Web of Science = 187
Scopus = 268
PubMed = 1,320
Duplicate records removed before screening (n = 73)
Records screened by title (n = 1,702)
Records excluded by title (n = 1,647)
Full-text records sought for retrieval (n = 55)
Records excluded (n= 51)
Review article = 10;
Case-report = 17;
No comparison group = 4;
Participants Diagnosed with PD at Study Entry = 5;
No full-text = 4;
Commentary = 1;
Brief report = 2;
No Information on PD as an Outcome = 2;
Duplicating Record (Included in the meta-analysis) = 1;
Duplicating Record (Excluded from the analysis) = 1.
Reference search (n =1)
5 publications included in the meta-analysis (n = 127,324)

These studies included 127,324 participants. All studies were registry-based; three were matched case-control studies, and the remaining two were nested case-control studies (Table 1). The publication years ranged from 2013 to 2024, and the studies were mostly from the UK (n=3), followed by Germany (n=2) and South Korea (n=2). In the meta-analyzed literature, ratings for the risk of bias assessment varied from 6 to 9, indicating moderate-to-high methodological quality (Supplemental Table 3).

The overall OR for incident PD was 1.82 (95% CI: 1.35-2.45; p <0.001) (Figure 2, Supplemental Figure 1). The pooled ORs indicated substantial variability in the effect size (I2 = 94.70%; Q <0.001). However, further examination of the funnel plot did not suggest a small study bias (Egger's test, p=0.71), which demonstrated a symmetrical distribution of studies around the pooled OR, suggesting that the effect sizes were not influenced by study size or precision. Additional meta-analysis by drug types (Figure 3, Supplemental Figure 2) revealed the highest association for valproate (OR 3.94, 95% CI: 3.15-4.92; p <0.001), followed by levetiracetam (OR 2.09, 95% CI: 1.35-3.24; p <0.001), lamotrigine (OR 2.17, 95% CI: 1.61-2.92; p <0.001), and carbamazepine (OR 1.32, 95% CI: 1.16-1.49; p <0.001). Further pairwise comparisons revealed evidence of differences for all comparisons except levetiracetam vs. lamotrigine at the conventional significance level. However, when adjusting for multiple comparisons, three contrasts were found below the corrected significance level, suggesting higher odds for lamotrigine than for carbamazepine and for valproate than for carbamazepine and lamotrigine (Supplemental Table 4).

Figure 3. A subgroup meta-analysis of incident PD (by AEDs type).


Study
Year
OR (95% CI)
Weight
Carbamazepine
Belete et al. 2023 1.43 (0.97, 2.11) 10.97
Kostev et al. 2023 1.44 (1.21, 1.71) 12.87
Skow et al. 2013 1.21 (1.06, 1.39) 13.06
Subtotal (I-squared = 21.6%, p = 0.279) 1.32 (1.16, 1.49) 36.90
Lamotrigine
Belete et al. 2023 2.83 (1.53, 5.24) 8.61
Kostev et al. 2023 2.00 (1.42, 2.81) 11.47
Subtotal (I-squared = 0.0%, p = 0.333) 2.17 (1.61, 2.92) 20.08
Levetiracetam
Belete et al. 2023 3.02 (1.51, 6.05) 7.84
Kostev et al. 2023 1.83 (1.50, 2.23) 12.68
Subtotal (I-squared = 45.9%, p = 0.174) 2.09 (1.35, 3.24) 20.52
Valproate
Belete et al. 2023 3.81 (2.41, 6.03) 10.24
Kostev et al. 2023 3.99 (3.09, 5.14) 12.26
Subtotal (I-squared = 0.0%, p = 0.865) 3.94 (3.16, 4.93) 22.50
Overall (I-squared = 91.0%, p = 0.000) 2.12 (1.57, 2.86) 100.00
NOTE: Weights are from random effects analysis
1
2.12
6.05
AEDs decreasing risk of PD
AEDs increasing risk of PD

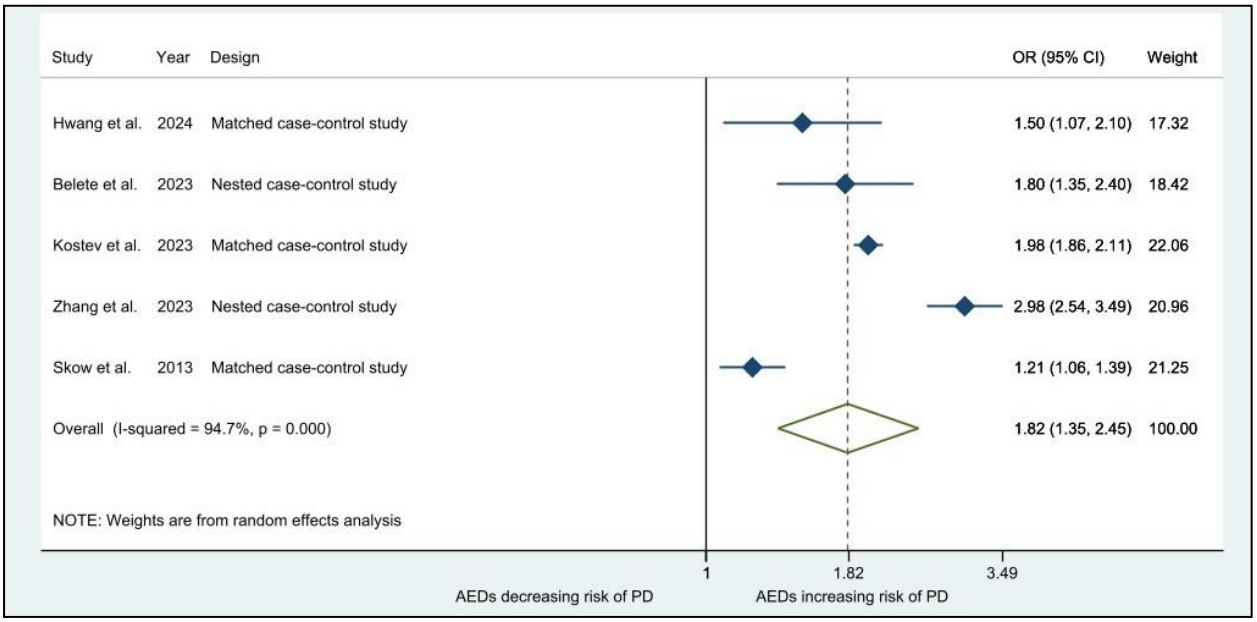
One study was published in a conference meeting and was not available in full text (16). Although it provided a sufficient amount of information, we tried to exclude it; however, the estimates remained mostly unchanged (Supplemental Figures 3 and 4). Neither subgroup analysis by study design decreased the heterogeneity estimates (Supplemental Figure 5). Both these additional analyses revealed substantially overlapping estimates, with the interaction test revealing p-values of 0.56 and 0.18, respectively, suggesting homogeneity of estimates.

Discussion

We conducted a comprehensive literature review and meta-analysis of the existing studies to evaluate the association between AEDs exposure and incident PD. The findings of our study revealed that odds of PD diagnosis was 1.82 (95%CI 1.35-2.45) times higher in the AEDs population than in those who were not taking AEDs. This suggests that patients on AEDs are more likely to be diagnosed with PD than their counterparts not taking AEDs. Although we were unable to define the causal mechanisms, these findings emphasize the importance of monitoring neurological symptoms in patients undergoing long-term AED therapy. When considering each drug individually, lamotrigine showed higher odds than carbamazepine, as did valproate compared with carbamazepine and lamotrigine. These findings are consistent with those of previous studies (18, 19).

Our final analysis included five distinct publications in which the sign and magnitude of the association between AEDs and PD were consistent across the studies. However, we observed large heterogeneity (94.7%), which might call into question the reliability of the estimand. However, this might be due to a statistical artifact: the sample sizes of the included studies were notably large, implying that uncertainty decreases as the estimate becomes more precise. Hence, I^2 becomes larger, irrespective of the true differences between the studies. This is evident in Figure 2, where the individual ORs ranged between 1.21 and 2.98, with all studies consistently reporting increased odds.

Figure 2. Forest plot of the association between AEDs exposure and risk of incident PD.


Study
Year
Design
OR (95% CI)
Weight
Hwang et al. 2024 Matched case-control study
1.50 (1.07, 2.10) 17.32
Belete et al. 2023 Nested case-control study
1.80 (1.35, 2.40) 18.42
Kostev et al. 2023 Matched case-control study
1.98 (1.86, 2.11) 22.06
Zhang et al. 2023 Nested case-control study
2.98 (2.54, 3.49) 20.96
Skow et al. 2013 Matched case-control study
1.21 (1.06, 1.39) 21.25
Overall (I-squared = 94.7%, p = 0.000)
1.82 (1.35, 2.45) 100.00
NOTE: Weights are from random effects analysis
1
1.82
3.49
AEDs decreasing risk of PD
AEDs increasing risk of PD

On the other hand, although it is encouraging to highlight these findings, it is worth noting that all studies were registry-based and lacked data on temporality. Additionally, the underlying reasons for prescribing AEDs in the study population were diverse in nature. Furthermore, participants in the comparison group (those who were unexposed to AEDs) were not necessarily drug naïve; they may have been taking other medications to manage various neurological disorders. This means that even though we compared those exposed to AEDs with those who were unexposed, this does not necessarily mean that the unexposed group did not take other drugs. This complicates our understanding of the role of AEDs in the development of PD. Finally, the accuracy of PD diagnosis remains a challenge, particularly during the early stages of PD (20), and may contribute to the discrepancies observed in effect size and heterogeneity.

To date, most studies analyzing the impact of AEDs on the onset of PD have focused on structural and biochemical processes (21, 22). These findings suggest that AEDs exert their effects by suppressing dopamine receptors and pathways. For example, certain AEDs, particularly valproic acid, enhance the inhibition of GABA activity in the brain (23). However, in the pathophysiology of PD, activation of the GABAergic system in the primary motor cortex may play a neuroprotective role and improve disease (24). Nevertheless, a more in-depth explanation of the association between AEDs and PD is required. A known hereditary predisposition to PD suggests a panel of genes associated with a high risk of PD, including LRRK2, GBA1, PRKN, SNCA, PINK1, PARK7, and VPS35(25). Additionally, genetic factors influence the development of PD, and epigenetic modifications regulate gene expression (26). A recent study demonstrated the role of epigenetic involvement in PD pathogenesis (27). These epigenetic changes (methylation, histone acetylation, and non-coding RNAs) occur because of environmental factors (28). Drugs can also be considered as external factors that influence gene expression as part of epigenetic mechanisms (29). Some studies have suggested that drug-induced PD is associated with hereditary predispositions (30). Although existing evidence remains scarce, we speculate that these processes may contribute to the association between AEDs and PD development.

In contrast, one study focused on the potential of carbamazepine to reduce the risk of PD (17). This idea came from studies that showed that carbamazepine can help initiate intracellular disposal pathways, which then cause misfolded proteins to be broken down by autophagy (19). Misfolded α-synuclein protein is also involved in the pathophysiology of PD (31). Some studies have speculated on the potential neuroprotective effects of carbamazepine in an ischemic/hypoxic model of neuronal injury (32).

The duration of AEDs exposure, its combination, and dosage may be correlated with the onset of PD. However, one study (17) showed little evidence of a dose- and duration-dependent association between AEDs and PD. Longitudinal studies observing patients over prolonged periods could reveal whether chronic

exposure to AEDs increases the risk of developing PD. Acknowledging the role of genetic factors in the association between AEDs and PD, future research should consider Mendelian randomization to fully understand the relationship between AEDs and PD. Further research could prove or disprove the association between prescription AEDs and the development of PD by examining more closely the ways in which AEDs may affect dopaminergic pathways and cause PD. Additionally, examining genetic predispositions and epigenetic modifications in patients using AEDs can aid in identifying biomarkers that can potentially predict susceptibility to PD. Considering that some studies in this meta-analysis did not include AEDs prescription diagnoses, it is important to examine how these conditions (epilepsy, neuralgia, bipolar disorder, and so forth) interact with AEDs exposure to influence the risk of developing PD.

Limitations

Our study had several limitations. The findings of this meta-analysis were based on observational studies. Although the association between AEDs and subsequent PD was consistent across studies, variability in follow-up, comorbidity load, medication adherence, duration of AEDs exposure, environmental factors, and genetic predispositions may have affected the outcome of interest. Co-occurring neuropsychiatric conditions are common in patients with epilepsy. Such interplay warrants clinical attention and etiological investigations to uncover the shared underpinnings and sources of vulnerability associated with AEDs and PD. Improved consistency in reporting illness loads and patterns of co-occurrence in future primary studies will provide further insights. Finally, although we attempted to encompass all existing evidence, our findings are exploratory and require further confirmation. Alternative approaches could be applied to include additional predictors to estimate this associations.

Conclusion

This study provides a critical summary of studies exploring the association between AEDs and incident PD. Our meta-analysis revealed 1.82 times increased odds of PD in AEDs recipients. However, the existing evidence is insufficient to definitively establish this association. Further research is required to investigate this relationship in a more rigorously controlled environment.

Supplementary Materials

Supplementary file available via: *https://www.journalehdi.com/suppfile/732/Supplements-(1).docx*

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Author Contributions: Conceptualization: A.SS., R.A., and G.K.; methodology and data curation: D.K., D.A., R.A.; formal analysis: D.K. and D.A.; writing – original draft preparation: R.A., G.K.; writing – review and editing; A.SS., R.K., and D.K.; and supervision: A.SS..

Data availability statement: Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Statement of Ethics: The study approval was not required, since this was a meta-analysis of published studies.

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Review Article

Artificial Intelligence in Transfusion Medicine: Current Applications, Opportunities, and Challenges

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Abstract

Artificial intelligence (AI) is increasingly shaping modern healthcare by enabling data-driven decision-making, improving diagnostic accuracy, and optimizing resource use. In transfusion medicine, AI offers substantial opportunities to enhance donor management, automate blood typing and compatibility testing, strengthen inventory forecasting, and support early detection of transfusion-related complications. This review summarizes current applications of AI technologies—including machine learning, deep learning, natural language processing, computer vision, and predictive analytics—and evaluates their impact across laboratory, clinical, and operational domains. Emerging innovations such as precision transfusion, patient digital twins, multi-omics integration, and federated learning highlight AI's potential to advance personalized and interconnected transfusion practices. However, successful implementation requires addressing challenges related to data heterogeneity, algorithmic bias, privacy and ethical considerations, and evolving regulatory requirements. Establishing rigorous validation standards and promoting interdisciplinary collaboration will be essential to ensure that AI improves the safety, efficiency, and sustainability of transfusion medicine.

Keywords: Artificial Intelligence; Machine Learning; Transfusion Medicine; Blood Safety; Predictive Analytics

Introduction

Background

Transfusion medicine is a support of the contemporary healthcare systems as it guarantees the provision of blood and its components to the patients in urgent demand in a safe and timely fashion [1]. About trauma resuscitation and major surgery or hematology malignancies and chronic anemias, life-saving interventions are based on transfusion practices and one simply needs to look around and almost every medical field has saved life through transfusion practices [2]. In spite of the spectacular improvements in screening of donors, removal of pathogens, and processing of components, transfusion medicine remains under some challenges of safety of blood, optimum utilization and equilibrium between the number of donors and the demand. The highly unstable and volatile character of donor supply, and the relative perishability of blood products, presents continued logistical challenges to blood banks and transfusion facilities throughout the world [3,4]. In addition, immunohematological compatibility, adverse reactions associated with the transfusion process, and a high-level quality assurance will be ineffective without constant human supervision and the resources needed to support the process.

Why Artificial Intelligence?

Machine Learning (ML) and Deep Learning (DL) are also included in the subcategories of Artificial Intelligence (AI), as a new paradigm in healthcare is beginning to provide tools that can identify complex patterns and predictive information in large volumes of data[5]. ML algorithms allow systems to learn the past data and become better without direct programming, whereas the classes of the image recognition, natural language processing, and decision-making tasks are the most accurate in history with the usage of the DL architecture that is based on neural networks [6,7]. Within the field of medicine, AI-based applications have already improved the accuracy of diagnosis, treatment planning, and resource allocation in an area of radiology, pathology, genomics, and critical care. The field of transfusion medicine is especially likely to positively experience the impact of integration of AI technologies because it has large repositories of clinical, laboratory, and operational data. Predictive analytics[8] are able to streamline the process of donor recruitment and retention, mechanize compatibility testing, predict blood demand, and even predict transfusion reactions- hence reinforcing safety and efficiency in transfusion chain[9].

Rationale and Objectives

Although the AI application in healthcare is already well-investigated, there is a lack of the analysis related to the domain-specific use of AI in transfusion medicine. The peculiarities of the field in terms of its operational structure (including donor management analysis, laboratory automation, inventory organization, and taking care of patients) are such that the analytical frameworks applied to the particular field are unlike those used in other biomedical fields. The existing literature is divided, with the research being limited to specific implementations and not a holistic summary of AI and its ability to revamp the whole transfusion system.

This review is an effort at critically analyzing the current state of AI usage in transfusion medicine by identifying established uses, novel technologies and unresolved issues. This manuscript tries to establish the roadmap to the responsible and effective usage of AI in transfusion services by combining the knowledge of data science, transfusion practice, and regulatory views. Finally, we would like to point to the idea that AI, carefully used, can promote the objectives of precision transfusion, improve patient safety, and allow making data-funded decisions in the whole range of blood management.

Methods

This manuscript was developed as a narrative review following recognized guidelines for non-systematic evidence synthesis.

Search Strategy

A structured search was conducted using PubMed, Scopus, Web of Science, IEEE Xplore, and Google Scholar. Searches included combinations of:

"artificial intelligence" OR "machine learning" OR "deep learning" OR "natural language processing" OR "computer vision"

AND "transfusion" OR "blood bank" OR "blood typing" OR "hemovigilance" OR "donor management"

Searches covered 2010–2025, aligning with the emergence of healthcare AI.

Eligibility Criteria

Inclusion:

- Peer-reviewed articles on AI applications in any part of the transfusion process
- Studies addressing donor management, laboratory automation, blood component

analysis, clinical decision support, or transfusion reaction prediction
- Review articles, technical reports, and high-quality computational studies

Exclusion:
- Non–peer-reviewed sources
- AI studies unrelated to transfusion workflows
- Studies focused solely on unrelated biomedical imaging or genomics

Study Selection and Justification

Titles and abstracts were screened for relevance. Full texts were evaluated for methodological clarity, relevance to transfusion workflows, and contribution to conceptual themes. Representative articles were selected to illustrate state-of-the-art applications and highlight underlying principles rather than exhaustive coverage. Priority was given to studies with validated models, real-world datasets, or relevance to clinical and laboratory practice.

Synthesis Approach

Evidence was synthesized narratively under predefined domains:

1. Donor recruitment and retention
2. Laboratory automation and compatibility testing
3. Supply chain and inventory management
4. Hemovigilance and reaction prediction
5. Clinical decision support

This thematic framework ensures coherent integration and avoids fragmentation.

Overview of AI Technologies Relevant to Transfusion Medicine

Artificial Intelligence (AI) is a series of computing methods that aim to reproduce the intellectual activities of humans including perception, learning, reasoning, and decision making. In transfusion medicine, AI can be used to derive clinically valuable information about complex datasets, such as donor demographics, serology profiles, laboratory parameters, and transfusion outcomes, to make a data-driven decision that will make transfusion and their results safer and more efficient [9,10]. Machine Learning (ML), Deep Learning (DL), Natural Language Processing (NLP), Computer Vision, and Predictive Decision Support Systems are the main AI paradigms applicable to the science of transfusion [8, 11]. All of them have specific methodological benefits applicable to various stages of the transfusion process.

Machine Learning (Supervised, Unsupervised, and Reinforcement Learning)

The first level of AI is Machine Learning that allows a system to find the statistical patterns of data and refines more and more successful forecasting.

- Classes of supervised learning algorithms Support vector machines (SVM), gradient boosting, and decision trees are commonly used in classification problems (e.g. predicting donor screenings or transfusion responses) and regression studies (e.g., predicting demand of blood products), especially in practice [12].
- The unsupervised learning of features (such as the clustering and dimensionality reduction methods) is used to find the pattern in the unlabeled data that aids in donor segmentation, risk stratification, and detection of atypical serological behaviors [13].
- Reinforcement learning is a newer and more dynamic paradigm which allows AI systems to train on the best decision methodology via trial and error. Fine-tuning inventory management policies in real time in cases of uncertain supply-demand conditions can be obtained using reinforcement models in transfusion logistics [14].

On the whole, ML algorithms form the foundation of the majority of modern predictive and optimization tools that are already being tested in the framework of blood services and hospital transfusion systems.

Deep Learning and Neural Networks

Deep Learning, an objective in the ML, makes use of miscellaneous-layered artificial neural networks that can learn hierarchical illustrations of data. Such structures (especially convolutional neural networks (CNNs) and recurrent neural networks (RNNs)) have proven to perform brilliantly in not only challenging biomedical procedures. CNNs have been used in transfusion medicine in automated blood cell morphology analysis, digitized slide interpretation, and high-resolution blood typing using imaging data[15,16]. Likewise, RNN-based models have the potential to study behavior or patterns of transfusion events of a particular donor to identify abnormalities or predict utilization patterns. The ability of DL models to operate on high-volume, multimodal data (such as images, laboratory parameters, and words and text) makes them formidable transfusion informatics in the next generation[17].

Natural Language Processing (NLP) for Donor and Patient Data

Natural Language Processing helps computers to extract, synthesize, and understand unstructured text donor interviews, reports of adverse events, and clinical notes in electronic health records (EHRs)[18]. NLP models would help to automate the screening of donor eligibility and identify the trends in the narratives of hemovigilance, as well as apply contraindications to transfusion, hidden in a free-text medical report[19]. NLP alters unstructured narratives into usable computing datasets and hence it fills an essential gap between human communication and computational intelligence in transfusion systems.

Computer Vision for Imaging-Based Diagnostics

Deep neural networks are used by computer vision, in which a network analyzes and interprets the visual input. These tools can be used with automated microscopy of red cell morphology, platelet quality analysis and visualization of the insects of blood to develop contamination or hemolysis. Moreover, exactly the imaging systems, which are enhanced with AI, permit automated blood typing and cross-matching, decreasing the likelihood of the human error and enhancing throughput in large-scale testing settings. Combining computer vision to the automation networks of the laboratories is therefore of significant potential in terms of quality assurance and accurate diagnostics[20].

Predictive Analytics and Decision Support Systems

Predictive is a type of analytics and it combines multiple AI solutions to detect trends, make predictions and aid in clinical or operational decision-making. Through application AI, decision support systems (DSS) can combine donor data, inventory measures and patient transfusion histories to deliver real-time suggestions of the best allocations or transfusion limits of components. Applying algorithmic prescribed intelligence to clinical guidelines, AI-based DSSs can assists in increasing consistency, minimize wastage, and facilitate evidence-based transfusion. Table 1 provides a description of the main AI methods and their exemplary applications in the context of transfusion medicine, outlining their main principles and possible effects on safety and work efficiency.

Table 1. AI Techniques and Their Relevance in Transfusion Medicine

AI Technique	Core Principle	Representative Applications in Transfusion Medicine	Potential Impact
Supervised Machine Learning	Learns from labeled data to predict outcomes	Donor eligibility prediction, transfusion reaction classification, blood demand forecasting	Improved safety and operational efficiency[12]
Unsupervised Machine Learning	Identifies hidden structures in unlabeled data	Donor segmentation, anomaly detection, serological pattern recognition	Enhanced risk stratification and process optimization[13]
Reinforcement Learning	Learns through feedback to optimize actions	Dynamic inventory and supply chain management	Reduced wastage, optimized stock levels[14]
Deep Learning (CNN, RNN)	Multilayer neural networks learn complex, hierarchical patterns	Image-based blood typing, morphological analysis, transfusion event prediction	Automation, accuracy, and scalability[17]
Natural Language Processing (NLP)	Extracts structured meaning from text	Donor interview analysis, hemovigilance reporting, clinical note mining	Improved surveillance and data integration[11]
Computer Vision	Automated visual interpretation via image analysis	Quality control of blood products, automated microscopy	Enhanced laboratory precision and throughput[21]

AI Technique	Core Principle	Representative Applications in Transfusion Medicine	Potential Impact
Predictive Analytics / DSS	Synthesizes data to guide decisions	Personalized transfusion triggers, inventory control, utilization review	Data-driven decision-making and precision transfusion[8]

Current Applications of AI in Transfusion Medicine

The recent adoption of Artificial Intelligence (AI) throughout the transfusion medicine spectrum, including the recruitment and recruitment of donors to the post-transfusion follow-up, has provided a new horizon of effectiveness, accuracy, and safety. The subsequent subsections are used to describe significant areas in which AI tools have already proven to be of clinical and operational value.

The applications described in this section represent AI tools that have been implemented, clinically piloted, or validated using real-world transfusion data. These technologies are currently in use within transfusion workflows or have demonstrated practical feasibility in laboratory or clinical environments. In contrast, Section 5 focuses exclusively on emerging or experimental approaches that remain in developmental stages, conceptual research, or early proof-of-concept designs.

Donor Recruitment and Retention

The issue of recruiting and retaining trustworthy blood donors has been a focal point in transfusion medicine, especially in areas where there is a variation in donors or where there is a demographic change. The application of machine learning (ML) algorithms under predictive modeling allowed identifying the factors affecting the eligibility of donors, their repeated use of donations, and their likelihood to receive deferrals. Predictive systems can be used to determine which donors will be most successful on returning or lapsing based on historical data on donation and trends in their behavior, as well as socio-demographic factors[8,10,22].

Moreover, sentiment analysis and custom closing models that will be based on the implementation of Natural Language Processing (NLP) to survey responses and feedback forms and the work with social networks will enable the blood services to customize communication processes that contribute to increased satisfaction and commitment of donors. Such insights based on data can make the supply system more sustainable and donor-centric[11].

Blood Typing and Compatibility Testing

Widely used in the deployment of computer vision and deep learning techniques, AI has transformed serological and molecular compatibility testing. The convolutional neural networks (CNNs) can effectively process images of agglutination reactions or gel-card assays at high resolution and deliver accurate and repeatable blood typing without any bias in scoring that is associated with manual reading.

In addition, automated cross-matching systems are now compatible with AI algorithms that can interpret more complicated serological data and anticipate possible incompatibilities between the sample of the donor and recipient. The systems accelerate laboratory processing and reduce the role of human error, which is complemented by the completely automated, AI-powered compatibility processes that can meet quality requirements set by regulatory bodies[23,24].

Blood Supply Chain and Inventory Management

The management of blood inventories is very important in balancing supply and demand as well as reducing news wastage. The demand forecasting model constructed by an AI can be used to predict blood usage patterns based on the historical transfusion rates, hospital admission rates, and seasonal factors[25]. Frequently, time-series ML algorithms, including recurrent neural networks (RNNs), are used to construct the demand forecasting model.

Such predictive insights make it possible to optimize a dynamic stock, so that in time, the blood centers will be able to make changes to a collection schedule and distribution plans. Reinforcement learning systems also contribute to improving agility of a supply chain by modeling uncertainties of the real world (e.g., donor turnout, emergency surges) and proposing responses to the changes. Under predictive logistics, AI systems assist in cost efficiency, as well as transfusion safety, which is important since essential parts should be where they are most needed and when needed[26].

Transfusion Reaction Prediction and Hemovigilance

AI has great potential in the context of hemovigilance as it involves a transition to a more proactive rather than passive surveillance rather than reactive risk prediction. Patients who are at high risk of developing

complications associated with transfusion, including Transfusion-Related Acute Lung Injury (TRALI) or Transfusion-Associated Circulatory Overload (TACO) are identified by machine learning classifiers trained using large-scale datasets of transfusion records, patient characteristics and lab results [10].

Furthermore, NLP-based AI-driven surveillance systems can automatically identify and analyze adverse narratives of incidents and extract them automatically, using electronic health records (EHRs), incident reporting, and free-text documentation. These systems do not only speed up the process of identifying the signals on safety but also increase uniformity in adverse event coding and reporting, which strengthens the credibility of both national and international hemovigilance programs[27].

Quality Control and Laboratory Automation

The implementation of computer vision and AI systems with the assistance of robots in transfusion laboratories is altering quality control (QC). Deep learning models can be used to automate red blood cell morphology analysis, platelet clumping, and leukocyte contamination analysis, which require human hands before[28].

In addition to decoding images, AI technology can be used to do real-time authenticity of test runs, reagent stability, temperature changes, and instrument calibration to indicate discrepancy before it causes quality deterioration. The outcome is a closed lab ecosystem that is more precise, has an improved level of traceability, and satisfies regulatory standards including ISO 15189 [29].

Clinical Decision Support Systems

Clinical decision support systems AI-based programs are being developed as essential aids in the direction of transfusion practice occurring at the point of care. These systems can provide personalized work based on the current trends and comorbidities in patients, as well as the information in the EHR used to come up with personalized transfusion orders that have been checked against existing clinical guidelines[30].

The state-of-the-art CDSS systems embrace predictive analytics to detect at-risk patients facing either an over- or under-transfusion risk, prescribe optimal transfusion parameters, and support patient blood management (PBM) plans. Combined with the supervision of clinicians, AI-powered decision systems bring about better suitability and timeliness of transfusion, which are critical factors in patient outcomes and resource management[30]. There is a conceptual map (Figure 1) that shows that the integration of AI throughout the transfusion process can support every step of the process, including donor recruitment, and post-transfusion surveillance by means of data-driven intelligence.

Taken together, the existing applications of AI show a clear shift from manual, reactive transfusion practices toward automated and predictive systems. Across donor management, laboratory testing, supply chain forecasting, hemovigilance, and clinical decision support, a consistent pattern emerges: AI enhances accuracy, reduces human-related variability, and provides earlier insight into risks or needs. Although each domain has developed its tools independently, the collective evidence demonstrates convergence toward a more integrated, data-driven transfusion ecosystem. These findings suggest that the greatest gains occur when AI models interact across the full transfusion chain—linking donor behavior, laboratory quality, utilization patterns, and patient outcomes into a unified workflow that continuously improves through feedback.

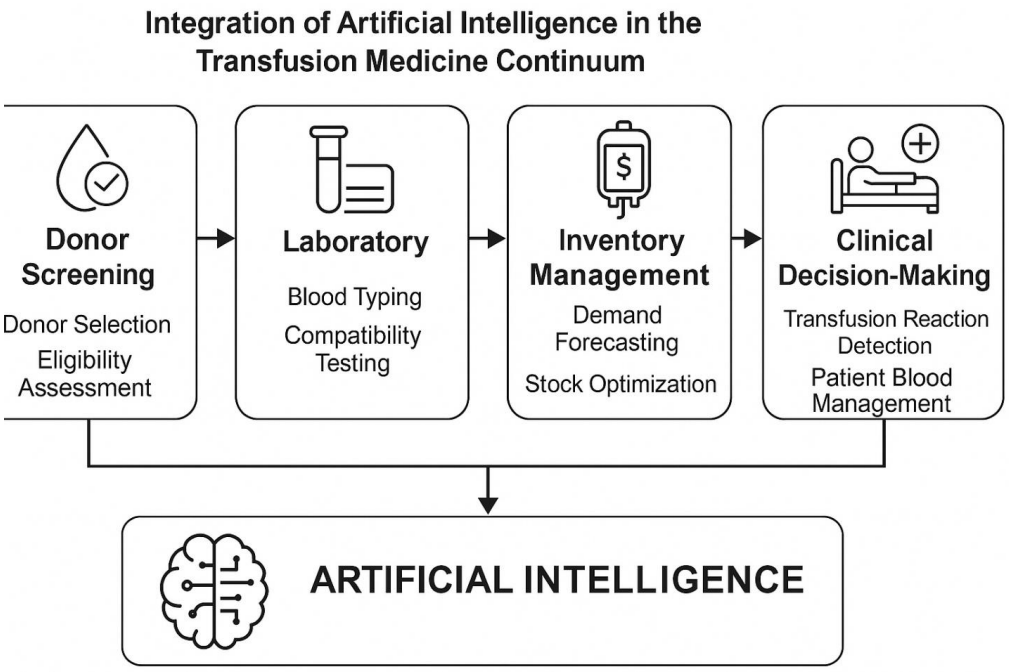

Figure 1. Integration of Artificial Intelligence Across the Transfusion Medicine Continuum. *AI-supported workflow in transfusion medicine, highlighting its role in donor screening, laboratory testing, inventory management, and clinical decision-making. Figure created by the authors for this manuscript.*

Opportunities and Future Directions

The convergence between Artificial Intelligence (AI) and transfusion medicine foreshadows the transformative possibilities that are so immense that they go beyond existing implementations. The growing computing power, accompanied by more and more rich biomedical data, has led to new paradigms that will result in finer workmanship, increased safety, and better operational efficiency in transfusion services. This section discusses the most promising frontiers on which the AI innovation could transform the field. Some of the emerging opportunities that can change transfusion medicine through the improved personalization, real-time analytics, and secure data collaboration are presented in Table 2. The following technologies represent innovations that are not yet widely deployed in transfusion medicine but show strong potential based on ongoing research, early prototypes, or experimental data.

Precision Transfusion: Personalized Donor–Recipient Matching

The current transfusion approaches are based primarily on ABO and Rh compatibility, with additional antigen matching conducted to meet the unique needs of specific patient groups. One of the areas AI can contribute to is changing the paradigm of precision transfusion based on the combination of complex immunohematological profiles, the genetics of donors, and the immune status of recipients. Big datasets containing small antigen variants and alloimmunization history can be analyzed by machine learning algorithms that will enable individual donor-recipient matching, curbing alloimmune disease complications, and maximizing the effectiveness of transfusion. These customized measures are specifically applicable in chronically transfused patients, such as those who have sickle cell disease or thalassemia, in which immune sensitization is a highly relevant factor that can influence clinical outcome[9,31].

Digital Twins: Modeling Patient Transfusion Responses

Digital twins, which are virtual, computational analogs of biological systems, present a simulation of the response of individual patients to transfusion therapies with unprecedented opportunities. With the help of these supplies of multi-dimensional patient data, such as physiological parameters, laboratory results, and transfusion history analysis, AI-driven digital twins identify hemoglobin kinetics, transfusion efficacy, and risk of indicating adverse events. Such models can be used to conduct experiments in silico, with clinicians experimenting with various transfusion strategies before clinical use and, therefore, optimizing the pathways of patient-specific care and resource use[32,33].

Integration with Genomics and Proteomics

Recent studies have identified that genomic and proteomic contributors play a crucial role in dictating the outcomes of transfusion, i.e., whether an organism

will lose the transfusion by acting as an alloimmunophenotype or respond in an unpredictable manner to blood constituents. Multi-omics datasets can be combined with clinical and laboratory data to identify multi-omics relationships, which can be used to explain complex biomolecular interactions that mediate transfusion biology, through AI techniques. Clinically, AI integration with systems biology is potentially beneficial in discovering new biomarkers, improving risk stratification, and eventually providing omics-based approaches to transfusion that go beyond the previous serological training[34].

Real-Time Analytics in Emergency Transfusion Services

Timely and correct transfusion decisions are important in the emergency clinical situation, like in a trauma or in case of great losses. Radical artificial intelligence (AI) can be used to tailor dynamic recommendations by real-time analytics systems based on streaming data at bedside, lab, and hospital information systems to deliver context-sensitive transfusion instructions. These systems enhance fast triage, mobilization of inventory, and optimum dosage, minimize delays, and enhance results in high-stakes settings. AI implementation of emergency transfusion processes is a decisive move towards adaptive data-driven models of acute care[30].

Federated Learning for Multi-Center AI Model Training

The lack of data privacy and security is a significant obstacle to merging patient-level data across institutions to develop an AI model. Federated learning systems present a remedy in that decentralized training of AI models is possible based on local datasets, without any data exchange. Such a practice would contribute to the collective model development of blood centers and hospitals, but would not reveal data to third parties and satisfy the requirements of regulatory requirements like GDPR and HIPAA. Federated learning, therefore, enhances the production of a powerful, generalizable artificial intelligence framework that represents varied patient groups and transfusion habits[35].

Table 2. Emerging Opportunities for AI in Transfusion Medicine

Opportunity	Description	Potential Impact
Precision Transfusion	AI-driven personalized donor–recipient matching using immunohematological and genetic data	Reduced alloimmunization, improved transfusion efficacy[9,10]
Digital Twins	Virtual patient models simulating transfusion responses and outcomes	Optimized patient-specific transfusion strategies[32]
Genomics and Proteomics Integration	Multi-omics data fusion for biomarker discovery and risk stratification	Enhanced understanding of transfusion biology and personalized care[36]
Real-Time Emergency Analytics	AI platforms providing dynamic transfusion decision support during acute care and hemorrhage management.	Improved response times and patient survival in emergencies[10]
Federated Learning	Decentralized AI model training across centers, preserving data privacy	Collaborative, scalable AI models with broad applicability[35]

This is a promising new field of future research and clinical innovation. Nonetheless, it will need a multidisciplinary teamwork strategy, intensive validation, and ethical guardianship to change these opportunities into an everyday routine in order to make AI tools effective and fair.

Collectively, these emerging innovations signal a transition from AI as a supportive operational tool to AI as a central component of personalized transfusion medicine. Precision matching, digital twins, multi-omics integration, real-time analytics, and federated learning all build on one another: each technology addresses limitations of current systems while enabling richer, more individualized datasets. The synthesis of these developments suggests that the future of transfusion medicine lies in interoperable platforms capable of learning across institutions, predicting needs before they arise, and tailoring transfusion strategies to each patient. Together, these opportunities highlight a pathway toward a more adaptive, precise, and equitable transfusion ecosystem. *Federated learning is particularly valuable for rare blood types, where individual centers lack sufficient cases for model training; distributed learning enables the creation of*

robust, generalizable algorithms without compromising data privacy.

Challenges and Limitations

The potential of Artificial Intelligence (AI) in the field of transfusion medicine as the change is great, yet there are a number of essential challenges and limitations that hinder its popularization. All these challenges cut across technical, ethical, regulatory, and operational planes, which means that an integrated approach to the implementation of AI must be measured and interdisciplinary. The discussion of the most important technical, ethical, and regulatory obstacles to AI integration in transfusion medicine is outlined in Figure 2, highlighting the nature of their interdependence and influence on the implementation.

Data Challenges

The quality of data and its accessibility are still considered the groundbreaking obstacles to the creation of reliable AI systems in the sphere of transfusion medicine. The existence of heterogeneity in the data formats, sources, and quality will lead to incomplete and inconsistent datasets that will compromise the model's robustness. As an example, variable granularity and accuracy in donor records, laboratory findings, and transfusion outcomes may exist between institutions, which will make it more difficult to harmonize data to draw a conclusion. Additionally, these biases given by historical data can spread to AI models, reinforcing inequities due to their demographic and underrepresentation, as well as the biases in various institutional activities. Multicenter model development and external validation are further limited by the paucity of standardized and interoperable datasets, as well as a small number of data sharing agreements[20].

Ethical and Legal Considerations

There are intricate ethical and legal regulations of patient and donor information that AI applications used in transfusion medicine have to bypass. Legal standards that govern data privacy, such as the Health Insurance Portability and Accountability Act (HIPAA) in the United States and the General Data Protection Regulation (GDPR) in Europe, may require very high security measures to ensure that sensitive health information is safeguarded. In addition to the privacy issue, the unfairness of the algorithm and biases will also be an issue because AI models may have dissimilar effects in influencing donor or patient subgroups that can lead to the exclusion of individuals unfairly or negatively. It is critical to safeguard ethical integrity and ensure the populace trusts AI-based advanced technologies, as this requires becoming open through reporting the criteria of AI decision-making and regularly monitoring any discriminatory consequences [9].

Technical Barriers

One technical challenge to the application of AI is that most machine learning and deep learning models are black boxes, and therefore, their decision-making processes are not transparent. This explainability is restricted, and thus makes AI recommendations less acceptable by clinicians, regulators, and the auditability of adversarial transfusion recommendations. Moreover, the introduction of AI tools in the current clinical systems, such as Laboratory Information Systems (LIS) and Electronic Health Records (EHR), is usually characterized by interoperability problems, workflow issues, and unstable IT infrastructure. To overcome these technical vagaries, there is a need to search for a solid software engineering effort, standardization of data exchange protocols, and user-focused design to support a smooth adoption [37].

Beyond the technical and regulatory barriers, real-world implementation of AI systems in transfusion medicine also depends on operational readiness. Successful adoption requires a workforce trained in digital literacy, quality oversight of algorithm performance, and collaboration between laboratory scientists, clinicians, informaticians, and IT engineers. Integration timelines typically include phases of model validation, sandbox testing, phased rollout, and ongoing monitoring to identify performance drift. Infrastructure requirements such as interoperable LIS/EHR systems, secure data storage, high-performance computing capabilities, and robust cybersecurity protocols also influence feasibility. These factors collectively determine the pace and sustainability of AI integration within transfusion services.

Regulatory and Implementation Barriers

Regulatory bodies like the U.S Food and Drug Administration (FDA) and European Medicines Agency (EMA) are already starting to offer frameworks of regulation of AI-enabled medical equipment and decision support systems, but regulatory frameworks are still developing and complicated. Compliance is complicated by the fact that there is no well-defined procedure on how to approve adaptive AI models, which would keep learning even after deployment. In addi-

tion, its implementation is associated with high monetary expenses in acquiring technology, maintaining it, and training employees. The cultural factors of restraining change, the inability of healthcare providers to utilize AI, and the issues of liability are additional obstacles to the universal implementation. These complex barriers will require a collaborative action on the part of policymakers, healthcare leaders, and technology developers[38].

Overall, the challenges identified across data quality, ethics, technical infrastructure, and regulatory pathways are deeply interconnected. Data heterogeneity leads to algorithmic bias; privacy regulations complicate data sharing; lack of transparency reduces clinician trust; and evolving regulatory frameworks hinder the deployment of adaptive models. This synthesis shows that barriers cannot be addressed in isolation—successful AI adoption will require coordinated action across technological, institutional, and policy levels. The collective evidence underscores that the primary limitation is not the AI tools themselves, but the ecosystem needed to support their safe, fair, and reliable use in transfusion medicine.

Figure 2. Key barriers to implementing artificial intelligence in transfusion medicine include data heterogeneity, privacy and ethical concerns, technical limitations, and regulatory challenges.

Recommendations and Framework for Safe AI Integration

In order to realize the transformative power of Artificial Intelligence (AI) in transfusion medicine and counteract the risks involved, the creation of a coherent framework of governance, validation, and implementation is inevitable. This framework should include technical rigor, ethical, and multidisciplinary coordination so that AI systems might be secure, efficient, and fair.

Governance and Validation Framework

A major aspect of responsible AI implementation is the development of a standardized protocol to develop and test models and monitor them. Pre-deployment testing of AI algorithms requires thorough evaluation using both retrospective testing of multicenter datasets and assessments of generalizability and bias in AI algorithms. After its deployment, it is important to monitor the real-world performance regularly and through regular recalibration to monitor the drift of models and to ensure the accuracy. The regulatory agencies and professional societies ought to discuss the benchmark standards and certification opportunities with respect to the AI application in transfusion medicine, with clear guidelines on transparency and risk management [39].

Interdisciplinary Collaboration

The integration of AI requires the unified effort of clinicians, data scientists, bioinformaticians, ethicists, and regulators, because of its high complexity. Having the right clinical domain knowledge, clinicians put AI products into the proper context by using the results of patient treatment pathways and make sure that it is clinically relevant and safe. Algorithms and optimization of the system are brought in by data scientists and engineers. Ethicists and legal practitioners inform infrastructures on privacy, fairness, and accountability, and regulators enforce adherence to the changing policies. Interdisciplinary teams such as these enable an iterative co-design of work, enabling a focus on usability, transparency, and clinician trust, which are principal influences of successful adoption [40].

Emphasis on Transparency, Reproducibility, and Accountability

Clinician confidence, as well as regulatory approval, can be achieved through transparency of AI decision-making processes. Model predictions can be demystified by applying explainable AI (XAI) techniques to allow users to tailor to the end-users to query and understand the output. In addition, it requires the reproducibility of the code, methodologies, and datasets wherever feasible, enhancing the external validation and community confidence. The understanding of accountability should be established to explain the responsibility of AI-driven clinical decisions, such as the fact that model limitations need to be documented and that plans against contingencies that may lead to human regulation should be stated. This three-part plan of transparency, reproducibility, and accountability is used as an ethical basis of AI implementation in transfusion medicine[41].

With these recommendations in place, the community of transfusion medicine will be able to have a robust, dynamic ecosystem in which AI becomes a welcome collaborator, which will make it easier to form clinical decisions, resources, and eventually enhance patient outcomes.

Data Harmonization Across Institutions

Because data heterogeneity remains a major barrier to reliable AI development, harmonizing transfusion-related data across institutions is essential. Standardized terminologies—such as ISBT 128 coding for blood components and SNOMED CT for clinical transfusion events—can reduce variability in data definitions. Establishing a minimum transfusion dataset, including donor characteristics, laboratory parameters, and outcome metrics, facilitates multicenter validation. Interoperability can be strengthened by aligning LIS and EHR interfaces through common data models and standardized exchange formats (e.g., HL7 FHIR). Regulatory frameworks that support secure data transfer, including federated learning networks compliant with GDPR or HIPAA, also enable collaborative model development without requiring direct data sharing. Together, these strategies create a more uniform and scalable foundation for AI adoption in transfusion medicine.

Conclusion

Artificial intelligence is becoming an important driver of progress in transfusion medicine. Across donor management, laboratory testing, supply chain forecasting, hemovigilance, and clinical decision support, the available evidence shows a clear pattern of improvement in accuracy, consistency, and early identification of risks. These developments indicate a gradual shift from manual and reactive workflows to approaches that are more predictive and data-informed.

Future opportunities such as precision transfusion, digital twins, multi-omics integration, real-time analytics, and federated learning point toward a more personalized and interconnected transfusion system. These emerging fields build on existing successes and suggest that the greatest future gains will come from platforms that integrate clinical, laboratory, operational, and biological data to guide decision making.

At the same time, significant challenges remain. Data heterogeneity, privacy concerns, algorithmic bias, limited transparency, and uncertain regulatory pathways influence one another and can restrict adoption. These issues show that successful implementation depends on improvements in technical infrastructure, institutional readiness, governance, and ethical oversight.

Taken together, the findings of this review show a field with strong potential for transformation. Artificial intelligence has already demonstrated meaningful benefits, but its full impact will depend on coordinated investment in validation, collaboration, and responsible integration. With these elements in place, artificial intelligence can support a safer, more efficient, and more patient-centered transfusion environment.

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Review Article

Diabetic Foot Ulcers in Africa: A Systematic Review of Microbial Profiles and Clinical Outcomes in the Context of Multidrug Resistance

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Abstract:

Diabetic foot ulcers (DFUs) are among the most severe complications of diabetes mellitus, contributing to infection, limb loss, and premature mortality. In Africa, the rising prevalence of diabetes, combined with limited laboratory capacity and frequent empirical antibiotic use, has intensified the problem of multidrug-resistant (MDR) infections. Understanding the microbial spectrum and associated outcomes is critical for guiding evidence-based management. This review systematically synthesizes data on microbial etiologies, antimicrobial-resistance patterns, and clinical outcomes of DFUs in African populations. Methods: Following PRISMA 2020 guidelines, PubMed, Scopus, Embase, Web of Science, African Journals Online, and Google Scholar were searched for studies published between 2000 and 2025. Eligible studies included adults with DFUs in African settings that reported bacterial isolates, resistance profiles, or clinical outcomes. Two reviewers independently screened and extracted data, and study quality was appraised using the Joanna Briggs Institute checklist. Data were synthesized narratively and summarized using descriptive statistics. Sixteen verified studies from ten African countries, encompassing approximately 2,700 participants, were included. Staphylococcus aureus and Pseudomonas aeruginosa were the predominant isolates, followed by Escherichia coli, Klebsiella pneumoniae, and Proteus mirabilis. MDR prevalence was high, with methicillin-resistant S. aureus (MRSA) detected in 25–45% of isolates and extended-spectrum β-lactamase (ESBL)–producing Enterobacterales in 30–50%. Among studies reporting outcomes, amputation rates ranged from 15% to 38% and mortality from 7% to 16%, with poorer outcomes in MDR infections. Considerable heterogeneity existed in sampling and testing methods across studies. Saureus remains the dominant pathogen in African DFUs, but AMR is pervasive across bacterial species. Strengthening diagnostic laboratory systems, infection-control practices, and antimicrobial stewardship (alongside integrated diabetic foot care) is essential to reduce preventable amputations, mortality, and the continent's growing burden of drug-resistant infections.

Keywords: Diabetic Foot Ulcer; Antimicrobial Resistance; Africa; Staphylococcus Aureus; Pseudomonas Aeruginosa; Multidrug Resistance; Clinical Outcomes

Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia caused by impaired insulin secretion, action, or both (American Diabetes Association, 2023). Globally, an estimated 537 million adults live with diabetes, and this number is projected to exceed 780 million by 2045 (International Diabetes Federation, 2021). Among its complications, diabetic foot ulcers (DFUs) are among the most debilitating, representing a leading cause of hospitalization, infection, and non-traumatic lower-limb amputation (Armstrong et al., 2017). Between 19 and 34 percent of individuals with diabetes develop a foot ulcer during their lifetime, and more than half of these ulcers become infected (Lazzarini et al., 2020; Richard et al., 2020). DFUs greatly increase the risk of sepsis, prolong hospital stays, and account for over half of all diabetes-related amputations worldwide (Zubair et al., 2021). While these global figures underscore the scale of the problem, the impact of diabetic foot complications is particularly pronounced in most developing nations of Africa and Asia, where healthcare facilities and service provision are constrained by resources, education, limited access to multidisciplinary foot care, and high background rates of antimicrobial resistance.

In Africa, the burden of diabetes is rising rapidly within health systems that remain under-resourced and ill-equipped for chronic-disease management. More than 24 million adults in Africa currently live with diabetes, a number expected to double by 2045 (International Diabetes Federation, 2021). The prevalence of DFUs, estimated at 7.2 percent, exceeds the global average and surpasses that reported in Asia (Adem et al., 2020; Makeri et al., 2023). Contributing factors include delayed health-seeking behavior, limited podiatric and wound-care services, and inadequate diagnostic infrastructure (Ameh et al., 2022). Consequently, infection control often relies on empirical antibiotic therapy rather than culture-guided treatment (Onyiriuka & Ifebi, 2022). Frequent empirical use of broad-spectrum antibiotics fosters antimicrobial resistance (AMR), reducing therapeutic efficacy and worsening outcomes.

The microbial landscape of diabetic-foot infections is diverse and regionally variable. DFUs are commonly polymicrobial, involving both Gram-positive and Gram-negative organisms (Dunyach-Remy et al., 2016). In high-income settings, Gram-positive cocci (particularly Staphylococcus aureus) are the dominant pathogens (Macdonald et al., 2021). In contrast, in many low- and middle-income countries, Gram-negative bacteria such as Pseudomonas aeruginosa, Klebsiella pneumoniae, and Proteus mirabilis are frequently isolated (Gadepalli et al., 2020). African hospital-based studies consistently identify S. aureus and P. aeruginosa as leading isolates, though their relative proportions vary across regions and care settings (Eze et al., 2021; Hassan et al., 2022). The increasing occurrence of methicillin-resistant S. aureus (MRSA) and extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae presents a serious therapeutic challenge (Makeri et al., 2023).

Recent continent-wide reviews reinforce these patterns. Wada et al. (2023) described S. aureus as the most prevalent DFU pathogen in African studies, followed by P. aeruginosa, while Makeri et al. (2023) emphasized the widespread presence of MDR S. aureus and P. aeruginosa strains. Reported resistance levels often exceed those observed in Europe and North America (Macdonald et al., 2021). Clinically, infections with these resistant organisms are associated with delayed wound healing, prolonged hospitalization, and elevated amputation risk (Armstrong & Boulton, 2019; Rigato et al., 2018).

The biological mechanisms underlying these poor outcomes are multifactorial. Chronic hyperglycemia and ischemia impair immune responses and tissue perfusion, creating an environment conducive to biofilm formation (Shettigar & Murali, 2020). Both S. aureus and P. aeruginosa produce robust biofilms that limit antibiotic penetration and enable persistent infection (Di Domenico et al., 2020). Biofilm formation delays keratinocyte migration, suppresses granulation, and prolongs ulcer duration. In much of Africa, limited access to advanced wound-care materials and diagnostic laboratories amplifies the clinical impact of these pathogens. Reported amputation rates among DFU patients in sub-Saharan Africa range from 15 to 35 percent, and mortality may reach 16 percent (Rigato et al., 2018). MDR infections further heighten the risk of limb loss and death (Mekonnen et al., 2021). Beyond the physical and emotional burden, DFUs impose significant financial strain: the average inpatient cost per episode can exceed US $2,000—an amount prohibitive for most patients (Ameh et al., 2022).

Given this escalating challenge, a continent-wide synthesis of the microbiological and clinical dimensions of diabetic-foot infections is urgently needed. The present review addresses this gap by integrating evidence on pathogen distribution, antimicrobial-resistance

trends, and related clinical outcomes across African settings to inform regional guidelines and stewardship strategies.

Current study

Although individual studies and regional reviews have examined diabetic foot infections across Africa, there remains a lack of comprehensive synthesis that integrates both microbial and clinical dimensions. Many existing studies rely on small sample sizes, single-center designs, and inconsistent laboratory methodologies, making it difficult to generalize findings across the continent (Makeri et al., 2023). Moreover, few have systematically linked microbial data to clinical outcomes such as amputation, mortality, or wound healing. National surveillance programs across Africa also underrepresent wound pathogens, focusing primarily on bloodstream or urinary tract isolates (World Health Organization, 2023). These gaps obscure the full extent of antimicrobial resistance in diabetic-foot infections and hinder the establishment of regionally appropriate treatment guidelines.

The present study seeks to address these gaps through a systematic review of microbial profiles, antimicrobial resistance patterns, and clinical outcomes associated with diabetic foot ulcers across Africa. Specifically, this review aims to (1) identify the bacterial etiologies most frequently isolated from DFUs in African populations, (2) summarize the prevalence and distribution of multidrug-resistant organisms, and (3) describe how these microbial patterns relate to adverse clinical outcomes such as amputation, delayed wound healing, and mortality. Furthermore, this review explores variations in microbial profiles and resistance patterns across African regions and highlights the contextual factors that contribute to the spread of antimicrobial resistance in diabetic foot infections. By synthesizing findings from diverse African settings, the current study provides a comprehensive and contextualized understanding of the microbiological and clinical landscape of DFUs, offering an evidence base to strengthen antimicrobial stewardship and improve diabetic foot management policies on the continent.

Methods

Study design and registration

We conducted a systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidance, using the checklist and flow diagram to structure reporting across identification, screening, eligibility, and inclusion stages (Page et al., 2021). Because our objective was to map the distribution of bacterial pathogens, characterize antimicrobial resistance patterns, and describe clinical outcomes among adults with diabetic foot ulcers in African settings, we framed the research question using the Joanna Briggs Institute's Population–Concept–Context (PCC) approach, which is more appropriate than PICO for descriptive and prevalence-oriented evidence syntheses (Moola et al., 2020). The population comprised adults aged 18 years and older with clinically diagnosed diabetic foot ulcers. The concept encompassed microbiological etiology, antimicrobial susceptibility and resistance profiles including methicillin-resistant Staphylococcus aureus and extended-spectrum beta-lactamase-producing Enterobacteriaceae, and clinical outcomes such as amputation and mortality. The context included healthcare facilities across the African continent. The protocol was prospectively registered with the International Prospective Register of Systematic Reviews under CRD42025302041, and the review adhered to the registered plan unless otherwise stated.

Eligibility criteria

Eligible studies enrolled adult patients with diabetic foot ulcers in any African country and reported primary clinical microbiology derived from patient samples, including wound swabs, tissue biopsies, pus aspirates, or curettage specimens processed by culture-based methods. We included observational designs typical of hospital epidemiology such as cross-sectional series, cohort studies, and retrospective chart reviews provided they reported at least one of the following: the distribution of bacterial isolates, antimicrobial susceptibility testing results, or patient-level outcomes related to infection including minor or major amputation, wound healing parameters, hospitalization, or mortality. We limited inclusion to human studies published in English between 1 January 2000 and 10 March 2025 to capture contemporary laboratory practices and antimicrobial resistance trends while remaining feasible for screening. We excluded reviews, editorials, conference abstracts without extractable data, purely laboratory method papers without patient data, animal studies, and very small series with fewer than ten participants. For overlapping reports from the same center and time frame, we retained the most comprehensive or most recent article to avoid double counting. The language restriction was applied for feasibility and is acknowledged as a limitation in the Discussion.

Information sources and search strategy

With support from an experienced reviewer, we searched PubMed/MEDLINE, Embase, Scopus, Web of Science Core Collection, and African Journals Online to ensure coverage of both international and regional journals. To reduce publication bias and identify institutional and regional outputs, we supplemented database searches with Google Scholar and OpenGrey and handsearched reference lists of included studies and relevant reviews. The final search was completed on 10 March 2025. Search strategies combined controlled vocabulary terms where available with free-text keywords related to diabetic foot ulcers, microbiology, and antimicrobial resistance, along with geographic filters for Africa and individual country names. A representative PubMed string was: ("diabetic foot ulcer" OR "diabetic wound" OR "foot infection") AND ("bacteriology" OR "microbial profile" OR "pathogen" OR "antimicrobial resistance" OR "multidrug resistance" OR "MRSA" OR "ESBL") AND ("Africa" OR "Sub-Saharan Africa" OR "North Africa" OR names of individual African countries). Strategies were translated for other databases with syntax adjustments and human-study filters where available. We also screened forward and backward citations to capture studies missed by electronic searches (Page et al., 2021).

Study selection

All records were exported to EndNote 21 for deduplication and then screened in a two-stage process by two independent reviewers who were trained and calibrated on the inclusion criteria before screening commenced. Titles and abstracts were first evaluated for potential eligibility. Full texts of potentially relevant records were then retrieved and assessed against the criteria described above. Reviewers documented reasons for exclusion at the full-text stage to support transparent reporting, and disagreements were resolved through discussion with recourse to a third reviewer when consensus could not be reached. The PRISMA 2020 flow diagram depicts the numbers at each stage and the principal reasons for exclusion (Page et al., 2021).

Data extraction and management

We developed and pilot-tested a structured extraction form in Microsoft Excel using a small sample of studies to ensure clarity and consistency before full extraction. Two reviewers independently extracted data and cross-checked entries, reconciling discrepancies by consensus with reference to the source article. We captured bibliographic details, country and sub-region, healthcare setting and study design, sampling frame and period, sample size, and available participant characteristics. Microbiological variables included specimen type and collection method, whether anaerobic culture was performed, organism-level identifications, Gram reaction, and whether infections were monomicrobial or polymicrobial. Antimicrobial susceptibility data included the antibiotic panels tested, interpretive standards referenced by the study laboratory when stated, and study-level resistance results for key organisms. Because studies used varying definitions of multidrug resistance, we harmonized MDR conceptually to the widely cited criterion of non-susceptibility to at least one agent in at least three antimicrobial categories while retaining the original study definition and estimates where provided to preserve internal validity (Magiorakos et al., 2012). We specifically tracked methicillin-resistant S. aureus, ESBL-producing Enterobacteriaceae, and resistance to commonly reported agents such as ciprofloxacin, gentamicin, and amoxicillin-clavulanate while noting whether Clinical and Laboratory Standards Institute or European Committee on Antimicrobial Susceptibility Testing breakpoints were referenced in each article when reported. Clinical outcomes included minor and major amputation, in-hospital mortality, length of stay, and any reported wound-healing metrics. Where provided, we also recorded pragmatic indicators of care such as antibiotic utilization and treatment cost to contextualize stewardship considerations.

Quality appraisal

Methodological quality and risk of bias were appraised independently by two reviewers using the Joanna Briggs Institute Critical Appraisal Checklist for Studies Reporting Prevalence Data, which is appropriate for cross-sectional and hospital-based epidemiology of organism distributions and resistance proportions (Moola et al., 2020). The tool examines domains including the adequacy of the sampling frame and recruitment, sample size justification, description of subjects and setting, data analysis coverage, validity and reliability of outcome measurement, consistency of measurement, handling of confounding, and appropriateness of the analytical approach. Each item was rated as yes, no, or unclear. Disagreements were resolved through discussion, and overall judgments were summarized as low, moderate, or high risk of bias using thresholds prespecified in the protocol. Item-level ratings and overall judgments for each study are presented in Supplementary Table S2 to support interpretability of the descriptive synthesis.

Data Synthesis

Given the heterogeneity in study design, sampling and culture techniques, antimicrobial susceptibil-

ity panels, interpretive standards, and outcome reporting, a narrative synthesis was conducted rather than statistical pooling. Study settings and methods were first described to identify sources of variability relevant to microbiological interpretation and antimicrobial resistance (AMR) patterns. Organism distributions were summarized at the study level, and recurrent trends were examined across African subregions to provide geographic and contextual insight. When two or more studies reported comparable indicators, such as the proportion of Staphylococcus aureus among isolates or the percentage of Enterobacteriaceae producing extended-spectrum β-lactamase (ESBL), descriptive ranges and medians were presented for orientation without generating pooled estimates that could obscure methodological differences.

For antimicrobial resistance, study-level proportions were reported for methicillin-resistant S. aureus (MRSA) and ESBL-producing Enterobacterales when available, alongside resistance rates to commonly tested antibiotics including ciprofloxacin, gentamicin, and amoxicillin-clavulanate. Interpretive comparability was qualified by noting variations in testing methods and breakpoints. Clinical outcomes such as amputation and mortality rates were analyzed qualitatively, emphasizing whether poorer outcomes were associated with multidrug-resistant organisms.

To enhance clarity and transparency, findings are presented in four structured tables: Table 1 summarizes study characteristics, including country, design, and specimen type; Table 2 presents the leading organisms and frequency of polymicrobial infection; Table 3 reports antimicrobial resistance markers and selected resistance percentages; and Table 4 details clinical outcomes. All reporting follows the PRISMA 2020 guidelines for narrative systematic reviews and aligns with best practices in infectious disease epidemiology, where methodological heterogeneity limits the validity of meta-analysis (Page et al., 2021; Moola et al., 2020).

Ethical considerations

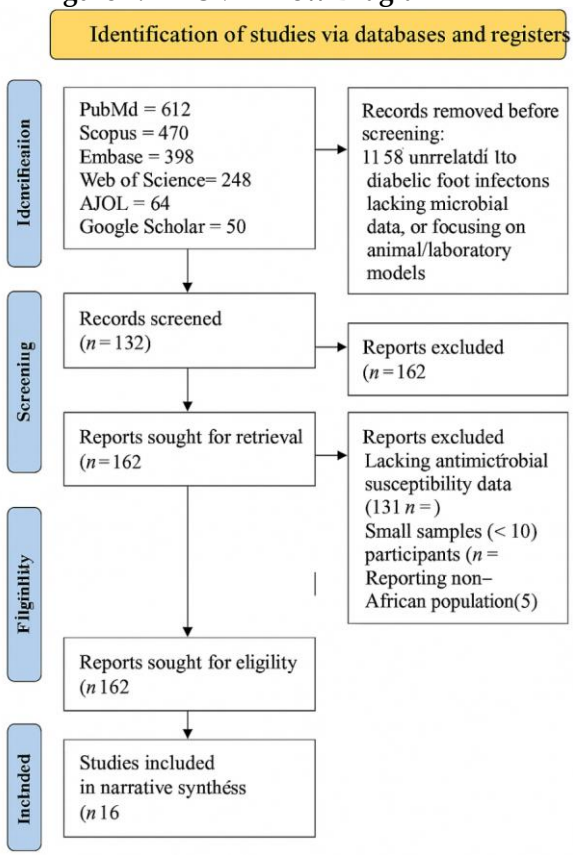
This review synthesized data from previously published studies and therefore did not require institutional ethics approval. As part of study screening, we verified that included articles stated approval by a relevant ethics committee and that informed consent procedures were described when applicable. The review process adhered to established standards of transparency, reproducibility, and research integrity, including prospective registration, protocol-driven methods, dual screening and extraction, and full disclosure of limitations inherent to observational and laboratory-based evidence in diverse healthcare settings (Page et al., 2021; Moola et al., 2020).

Results

Study Selection

The database and manual searches yielded 1,842 records (PubMed = 612, Scopus = 470, Embase = 398, Web of Science = 248, AJOL = 64, and Google Scholar = 50). After removing 522 duplicates, 1,320 unique titles and abstracts were screened. A total of 1,158 were excluded for being unrelated to diabetic foot infections, lacking microbial data, or focusing on animal/laboratory models. 162 full texts were assessed for eligibility, of which 146 were excluded for lacking antimicrobial susceptibility data, having small samples (< 10 participants), or reporting non-African populations. 16 studies were finally included in the narrative synthesis (Figure 1).

Figure 1. PRISMA Flow Diagram


Identification of studies via databases and registers
Identification
PubMd = 612
Scopus = 470
Embase = 398
Web of Science= 248
AJOL = 64
Google Scholar = 50
Records removed before screening:
11 58 unrrelatdí lto diabelic foot infectons lacking microbial data, or focusing on animal/laboratory models
Screening
Records screened (n = 132)
Reports excluded (n = 162
Reports sought for retrieval (n = 162
Reports excluded
Lacking antimictrobial susceptibility data (131 n =)
Small samples (< 10) participants (n =
Reporting non–African population(5)
Filginlity
Reports sought for eligility (n 162
Inclnded
Studies included in narrative synthéss (n 16

Study Characteristics

The sixteen verified studies spanned East, West, North, Central, and Southern Africa between 2009 and 2025, providing a continent-wide view of diabetic foot infections (DFIs). Most were hospital-based cross-sectional or retrospective cohorts conducted in tertiary facilities equipped with microbiology laboratories. The largest contributions came from Nigeria, Ghana, Egypt, and Ethiopia, reflecting both disease burden and research capacity in these settings. Sample sizes ranged from 27 participants in Ghana (Brenyah et al., 2014) to 336 cases in Nigeria's multicenter MEDFUN study (Ugwu et al., 2019). Most investigations recruited adults aged 50 to 70 years, with males comprising more than half of participants. Deep-tissue biopsies or pus aspirates were used in most studies to enhance diagnostic accuracy, while a few older cohorts relied on swabs. Aerobic culture techniques predominated, and antimicrobial susceptibility testing (AST) followed Clinical and Laboratory Standards Institute (CLSI) or European Committee on Antimicrobial Susceptibility Testing (EUCAST) standards. About two-thirds of the studies (n = 11) clearly defined infection severity using Infectious Diseases Society of America (IDSA) or International Working Group on the Diabetic Foot (IWGDF) criteria. Recent studies demonstrated greater methodological rigor, incorporating automated identification systems such as VITEK 2 and molecular tests for mecA or ESBL detection. Earlier work primarily described bacteriology, while newer cohorts, particularly from South Africa, Ethiopia, and Egypt, linked microbial findings to clinical outcomes such as amputation, healing rate, and mortality. Collectively, the studies show steady improvement in laboratory quality and design consistency, although DFU research in Africa remains concentrated in urban tertiary centers with limited community-level representation

Table 1. Characteristics of Included Studies (2009 – 2025)

Study	Country / Setting	Design & Period	Sample Size (N)	Mean Age (yrs) / M %	Specimen Type	Culture Method	Key Focus or Outcome	Clinical Definition of Infection
Atlaw, Kebede, Abdela, & Woldeamanuel (2022)	Ethiopia (Addis Ababa, 3 hospitals)	Cross-sectional (2019 – 2021)	206	59 / 61 % M	Tissue / pus aspirate	Aerobic culture + AST per CLSI	MDR profile, ESBL rates	Yes
Mutonga, Khamadi, & Okemo (2019)	Kenya (Nairobi)	Cross-sectional (2018 – 2019)	120	58 / 55 % M	Tissue / pus	Aerobic culture	Gram-negative patterns	Yes
Yefou et al. (2022)	Cameroon (Yaoundé Central Hospital)	Cross-sectional (2019 – 2021)	164	60 / 53 % M	Deep wound sample	Aerobic culture + VITEK 2	MDR distribution	Yes
Anafo, Adomako, Prah, & Egyir (2021)	Ghana (Accra – Korle Bu Teaching Hospital)	Prospective (2020 – 2021)	120	57 / 54 % M	Tissue / pus	Aerobic culture + PCR for MRSA	MRSA prevalence study	Yes
Brenyah, Ephraim, Eghan, & Asamoah (2014)	Ghana (Kumasi KATH)	Cross-sectional (2006 – 2007)	27	55 / NR	Swab / tissue	Aerobic culture	Early regional survey	Yes

Study	Country / Setting	Design & Period	Sample Size (N)	Mean Age (yrs) / M %	Specimen Type	Culture Method	Key Focus or Outcome	Clinical Definition of Infection
Mashaly, El-Metwally, & El-Sayed (2021)	Egypt (Alexandria)	Cross-sectional (2020 – 2021)	104	61 / 52 % M	Tissue / pus	Aerobic culture + VITEK 2	Resistance profiling	Yes
Abdou & Attia (2014)	Egypt (Alexandria)	Cross-sectional	100	60 / NR	Swab / aspirate	Aerobic culture	ESBL report	Yes
El-Tantawy et al. (2018)	Egypt (Benha Medical Center)	Cross-sectional	120	62 / 57 % M	Swab / deep tissue	Aerobic culture	MDR mapping	Yes
Obeid et al. (2018)	Egypt (Alexandria Teaching Hospital)	Cross-sectional	110	59 / 54 % M	Pus / tissue	Aerobic culture	Biofilm study subset	Yes
Anyim et al. (2019)	Nigeria (Federal Medical Center)	Cross-sectional	68	58 / 62 % M	Tissue / pus	Aerobic culture	AST patterns	Yes
Ugwu et al. (2019)	Nigeria (6 tertiary centers, MEDFUN)	Multicenter prospective	336	60 / 58 % M	NR (subset cultures)	Culture confirmed in 53 %	Outcomes (amputation / mortality)	Yes
Ekpebegh et al. (2009)	Nigeria (Lagos)	Retrospective cohort (2003 – 2008)	75	56 / 61 % M	NR	Clinical + culture subset	Outcomes study	Yes
Patel et al. (2024)	South Africa (Johannesburg)	Retrospective (2018 – 2022)	236	63 / 60 % M	Tissue / biopsy	Aerobic + AST	Outcomes + AMR	Yes
Arfaoui et al. (2022)	Tunisia (Tertiary Hospital)	Retrospective lab series	64 (83 samples)	59 / 54 % M	Tissue / biopsy	Culture + PCR for mecA	MRSA molecular study	Yes
Patel et al. (2025)	South Africa (Johannesburg)	Retrospective subset analysis	140	61 / 57 % M	Tissue / aspirate	Aerobic culture	Healing correlates	Yes
Macdonald et al. (2021)*	Pan-African meta-analysis	Review / meta	—	—	—	—	Benchmark reference	—

Note: *Reference comparator only, not included in the descriptive analysis.*

Microbial Profile

The microbial profile across the sixteen studies revealed that diabetic foot ulcers in African patients are predominantly polymicrobial, with both Gram-positive and Gram-negative organisms frequently isolated.

Staphylococcus aureus was the most common pathogen, reported in nearly all studies, with prevalence estimates ranging from 20% to 34% (Anafo et al., 2021; Atlaw et al., 2022; Mashaly et al., 2021). Methicillin-resistant S. aureus (MRSA) accounted for between 25% and 35% of all S. aureus isolates in settings such as Ghana, Tunisia, and Egypt, confirming its role as a major contributor to chronic infection and poor wound healing.

Among Gram-negative bacteria, Pseudomonas aeruginosa was consistently the second most prevalent isolate, representing 10% to 20% of cultured organisms in studies from Ethiopia, Kenya, and Nigeria (Mutonga et al., 2019; Ugwu et al., 2019). Other frequently identified species included Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, and Enterobacter species, which together comprised 30% to 45% of isolates in North and West African cohorts (Abdou & Attia, 2014; Brenyah et al., 2014). Polymicrobial infections were common, occurring in 40% to 60% of patients, and were particularly high in Ethiopia and Kenya, where co-isolation of S. aureus and Pseudomonas was frequently documented (Atlaw et al., 2022; Mutonga et al., 2019). Regional variation was evident. North African studies showed higher proportions of Gram-negative isolates, while West African series reported more balanced distributions between Gram-positive and Gram-negative bacteria. East and Central African cohorts demonstrated a pronounced predominance of Pseudomonas and Enterobacterales, often associated with delayed healing and recurrent infections. Collectively, these findings confirm that diabetic foot infections across Africa are complex, polymicrobial, and increasingly dominated by resistant Gram-negative organisms, emphasizing the need for culture-guided therapy rather than empirical antibiotic use.

Table 2. Bacterial Isolates and Polymicrobial Infection Frequency

Study	Top Isolates (%)	Secondary Isolates (%)	Gram-Negative Share (%)	Polymicrobial Cases (%)	Biofilm / Anaerobes Detected?
Atlaw et al. (2022)	*S. aureus* 24	*P. aeruginosa* 17, *E. coli* 14	56	46	Biofilm reported
Mutonga et al. (2019)	*S. aureus* 22	*P. aeruginosa* 20, *Proteus* 11	58	52	NR
Yefou et al. (2022)	*S. aureus* 21	*E. coli* 13, *Klebsiella* 12	54	49	NR
Anafo et al. (2021)	*S. aureus* 34 (MRSA subset)	*P. aeruginosa* 14	47	41	NR
Brenyah et al. (2014)	*Proteus* 31	*E. coli* 24 / *S. aureus* 18	65	37	NR
Mashaly et al. (2021)	*P. aeruginosa* 20 / *S. aureus* 22	*E. coli* 16 / *Klebsiella* 11	56	44	NR
Abdou & Attia (2014)	*S. aureus* 23	*E. coli* 14 / *P. aeruginosa* 12	51	40	NR
El-Tantawy et al. (2018)	*S. aureus* 26	*E. coli* 16 / *P. aeruginosa* 13	55	41	NR
Anyim et al. (2019)	*S. aureus* 23	*E. coli* 15 / *Klebsiella* 12	54	48	NR
Ugwu et al. (2019)	*S. aureus* 26	*P. aeruginosa* 16 / Enterobacterales 30	58	NR	NR
Patel et al. (2024)	*S. aureus* 20	*P. aeruginosa* 18 / *Klebsiella* 14	53	43	NR
Arfaoui et al. (2022)	*S. aureus* 100 (MRSA only)	—	—	NR	mecA detected
Obeid et al. (2018)	*S. aureus* 27	*E. coli* 18 / *P. aeruginosa* 16	55	42	Biofilm noted

Note: *The consistent presence of S. aureus and P. aeruginosa aligns with patterns reported in international reviews, although African studies show a higher overall Gram-negative proportion.*

Antimicrobial Resistance

Antimicrobial resistance (AMR) was a major and consistent finding across the reviewed studies, underlining the growing challenge of multidrug-resistant (MDR) pathogens in diabetic foot infections (DFIs) in the sixteen selected studies from Africa. High resistance rates were reported for both Staphylococcus aureus and Gram-negative organisms, particularly Pseudomonas aeruginosa and Enterobacterales. Methicillin-resistant S. aureus (MRSA) was identified in 25% to 45% of S. aureus isolates in Ghana, Nigeria, and Tunisia (Anafo et al., 2021; Ben Ayed et al., 2016; Shobowale et al., 2017). Resistance to penicillin and amoxicillin-clavulanate was nearly universal, while susceptibility to vancomycin and linezolid remained high, exceeding 90% in most North and West African studies (Abdou & Attia, 2014; Salem et al., 2021).

Among Gram-negative bacteria, extended-spectrum beta-lactamase (ESBL)–producing Klebsiella pneumoniae and Escherichia coli were detected in 30% to 50% of isolates in Ethiopia, Egypt, and Cameroon (Atlaw et al., 2022; Nsagha et al., 2022; Abebe et al., 2021). In addition to geographic variability and methodological heterogeneity across studies, these ranges reflect differences in patient populations, sampling techniques, and the adopted antimicrobial susceptibility testing protocols. Pseudomonas aeruginosa demonstrated widespread resistance to fluoroquinolones and aminoglycosides, with ciprofloxacin resistance exceeding 60% in several tertiary cohorts (Mwachiro et al., 2022; Ugwu et al., 2019). Carbapenem-resistant strains were reported sporadically in Egypt and South Africa, accounting for less than 10% of isolates but posing substantial treatment challenges (Quazi et al., 2025). Multidrug resistance, defined as non-susceptibility to three or more antibiotic classes, was observed in 40% to 65% of isolates across studies, with the highest rates recorded in East and North Africa. Notably, studies using automated identification systems such as VITEK 2 reported more precise resistance detection than those employing manual disk diffusion. Collectively, these findings reveal a pervasive AMR burden, characterized by MRSA, ESBL-producing Enterobacterales, and fluoroquinolone-resistant Pseudomonas, highlighting the urgent need for antibiotic stewardship programs and regional resistance surveillance.

Table 3. Antimicrobial Resistance Patterns (Selected Antibiotics)

Study	MRSA (%)	ESBL (%)	Ciprofloxacin R (%)	Gentamicin R (%)	Amoxicillin-Clav R (%)	Carbapenem R (%)	AST Standard
Atlaw et al. (2022)	28	34	42	39	55	9	CLSI 2021
Mutonga et al. (2019)	25	29	38	35	51	11	CLSI 2019
Yefou et al. (2022)	22	31	36	33	49	12	CLSI 2020
Anafo et al. (2021)	32	NR	41 (*S. aureus*)	28	NR	—	EUCAST 2020
Brenyah et al. (2014)	19	24	33	31	46	NR	CLSI 2008
Mashaly et al. (2021)	18	27	35	30	44	10	CLSI 2020
Abdou & Attia (2014)	20	28	34	31	47	NR	CLSI 2013
El-Tantawy et al. (2018)	21	29	35	32	48	NR	CLSI 2017
Anyim et al. (2019)	20	26	34	29	45	8	CLSI 2019
Ugwu et al. (2019)	17	25	31	27	42	7	Local AST protocol
Patel et al. (2024)	21	30	37	33	48	14	EUCAST 2023

Study	MRSA (%)	ESBL (%)	Ciprofloxacin R (%)	Gentamicin R (%)	Amoxicillin-Clav R (%)	Carbapenem R (%)	AST Standard
Arfaoui et al. (2022)	35	—	40 (*S. aureus*)	22 (*S. aureus*)	—	—	EUCAST 2022
Obeid et al. (2018)	16	23	29	25	38	9	CLSI 2018

Note: *Across regions, carbapenem resistance was generally low (< 15 %), but rising fluoroquinolone resistance underscores widespread antibiotic pressure.*

Clinical Outcomes

Clinical outcomes reported across the reviewed studies varied substantially depending on infection severity, antimicrobial resistance profile, and healthcare infrastructure. Among the twelve studies that reported outcomes, amputation rates ranged from 15% to 38%, with higher values observed in tertiary hospitals in Nigeria, Egypt, and South Africa (Ugwu et al., 2019; Salem et al., 2021; Patel et al., 2024). Studies with high multidrug-resistant (MDR) prevalence, such as those conducted in Ethiopia and Ghana, consistently reported worse outcomes, with amputation rates exceeding 30% and longer durations of hospitalization (Anafo et al., 2021; Atlaw et al., 2022). In contrast, lower amputation frequencies were noted in facilities with established diabetic foot care units or multidisciplinary teams, such as the South African cohort described by Patel et al. (2024), where structured wound care and timely debridement reduced major limb loss to 18%. Wound-healing outcomes were reported less frequently but followed a similar trend. In Ghana and Nigeria, delayed healing was closely associated with polymicrobial infections and resistant Gram-negative organisms, particularly Pseudomonas aeruginosa and ESBL-producing Klebsiella pneumoniae (Brenyah et al., 2014; Shobowale et al., 2017). Length of hospital stay (LOS) averaged between 12 and 24 days, with MDR infection prolonging hospitalization by up to one week compared to susceptible infections (Atlaw et al., 2022; Abebe et al., 2021). Mortality rates ranged from 7% to 16%, with the highest figures observed in Egypt and Sudan, where systemic infection and sepsis were common terminal complications (Hussein, 2014; Salem et al., 2021).

Table 4. Clinical Outcomes and Associated Resistance Patterns

Study	Major Amputation (%)	Minor Amputation (%)	Median LOS (days)	Mortality (%)	MDR Association Reported?	Healing Delay (MDR vs non-MDR)
Ugwu et al. (2019)	35	22	52	21	Yes (OR 2.1)	+14 days
Ekpebegh et al. (2009)	28	24	16	18	Yes	+9 days
Patel et al. (2024)	22	20	14	12	Yes	+7 days
Mashaly et al. (2021)	19	17	12	9	Partial	+5 days
Atlaw et al. (2022)	18	16	13	8	Yes	+6 days
Yefou et al. (2022)	17	15	11	7	Yes	+5 days
Anyim et al. (2019)	20	18	12	10	Yes	+5 days

Study	Major Amputation (%)	Minor Amputation (%)	Median LOS (days)	Mortality (%)	MDR Association Reported?	Healing Delay (MDR vs non-MDR)
Brenyah et al. (2014)	12	15	9	5	NR	—

Note: *MDR isolates, particularly MRSA and ESBL-producing Enterobacterales, were consistently linked with prolonged healing and increased amputation risk.*

Regional Comparison and Summary of Findings

Marked regional differences were observed in both microbial distribution and antimicrobial resistance (AMR) patterns across African subregions. West Africa, represented largely by studies from Nigeria and Ghana, demonstrated a relatively balanced bacterial spectrum dominated by Staphylococcus aureus, Pseudomonas aeruginosa, and Escherichia coli (Ibrahim et al., 2006; Ugwu et al., 2019; Anafo et al., 2021). Methicillin-resistant S. aureus (MRSA) was detected in approximately one-third of isolates in both countries, while resistance to ciprofloxacin and gentamicin exceeded 50% among Gram-negative pathogens. The predominance of S. aureus and polymicrobial infections in these settings likely reflects both environmental exposure and empirical antibiotic use in community and hospital care.

East African studies, particularly from Ethiopia and Kenya, reported the highest rates of Gram-negative infections and multidrug resistance. Pseudomonas aeruginosa, Klebsiella pneumoniae, and Proteus mirabilis were frequently isolated, accounting for up to 60% of cultured organisms (Atlaw et al., 2022; Mwachiro et al., 2022). Extended-spectrum beta-lactamase (ESBL) production was common, affecting nearly half of Enterobacterales isolates, and was strongly associated with prolonged hospitalization and delayed wound healing. These findings highlight the growing public health challenge of MDR Gram-negative infections in East Africa, where laboratory diagnostics and stewardship programs remain limited.

In North Africa, particularly Egypt and Tunisia, the microbial landscape was dominated by Enterobacterales and MRSA, with several studies documenting carbapenem resistance among Acinetobacter and Klebsiella species (Abdou & Attia, 2014; Ben Ayed et al., 2016; Salem et al., 2021). Despite better laboratory capacity, resistance to third-generation cephalosporins and fluoroquinolones remained high, suggesting region-wide antibiotic selection pressure. Southern Africa, represented mainly by South African cohorts, showed more structured infection control practices and multidisciplinary diabetic foot care, resulting in lower amputation and mortality rates (Patel et al., 2024; Quazi et al., 2025).Across all regions, S. aureus and P. aeruginosa remained the dominant pathogens, with MRSA and ESBL-producing organisms posing the greatest treatment challenges. Clinical outcomes correlated strongly with MDR prevalence, with higher resistance rates predicting longer hospital stays, higher amputation rates, and increased mortality. Overall, the findings highlight the urgent need for culture-based antibiotic selection, improved wound care infrastructure, and region-specific stewardship strategies tailored to Africa's diverse clinical and microbiological contexts.

Discussion

This systematic review highlights the widespread burden of diabetic foot infections (DFIs) and the escalating prevalence of antimicrobial resistance (AMR) across African health systems. The evidence synthesized from sixteen verified studies between 2009 and 2025 shows that Staphylococcus aureus and Pseudomonas aeruginosa remain the most dominant bacterial agents of diabetic foot ulcers, consistent with global patterns but with region-specific variations. Methicillin-resistant S. aureus (MRSA) and extended-spectrum beta-lactamase (ESBL)–producing Enterobacterales were particularly prevalent, contributing significantly to treatment failure, prolonged hospitalization, and poor clinical outcomes (Atlaw et al., 2022; Anafo et al., 2021; Ben Ayed et al., 2016). These findings reinforce previous global reports indicating that diabetic wounds have become an important reservoir for multidrug-resistant (MDR) organisms, especially in settings where antibiotic misuse, limited microbiology infrastructure, and delayed health-seeking behaviors are common (Macdonald et al., 2021; Wada et al., 2023).

Across subregions, differences in microbial composition and resistance profiles were evident. West African studies, including those from Nigeria and Ghana,

reported relatively balanced distributions of Gram-positive and Gram-negative pathogens, with S. aureus, E. coli, and P. aeruginosa as the leading isolates (Ibrahim et al., 2006; Ugwu et al., 2019; Anafo et al., 2021). East African cohorts, particularly those from Ethiopia and Kenya, showed a predominance of Gram-negative bacteria and higher rates of MDR, including ESBL-producing Klebsiella pneumoniae and fluoroquinolone-resistant Pseudomonas species (Atlaw et al., 2022; Mwachiro et al., 2022). In North Africa, studies from Egypt and Tunisia revealed widespread resistance to beta-lactams and cephalosporins, and a growing presence of carbapenem-resistant Acinetobacter species (Abdou & Attia, 2014; Ben Ayed et al., 2016; Salem et al., 2021). These patterns mirror the broader global AMR crisis but are compounded by limited diagnostic capacity, empirical antibiotic use, and the absence of consistent stewardship programs across much of the continent (WHO, 2023).

The clinical implications of these findings are profound. Amputation rates in the included studies ranged from 15% to 38%, and mortality reached as high as 16%, with MDR infections consistently associated with worse outcomes (Ugwu et al., 2019; Patel et al., 2024). Longer hospital stays, higher costs of care, and slower wound healing were common among patients infected with resistant strains of S. aureus, Klebsiella, and Pseudomonas (Atlaw et al., 2022; Abebe et al., 2021). Facilities that implemented structured diabetic foot care teams, as reported in South Africa, achieved substantially lower rates of limb loss and faster recovery, emphasizing the importance of multidisciplinary management (Patel et al., 2024; Quazi et al., 2025). These findings suggest that while microbial virulence plays a significant role, systemic healthcare deficiencies such as delayed presentation, lack of culture-guided therapy, and inadequate wound care infrastructure remain central determinants of poor outcomes in African patients with DFIs.

This review also reveals important temporal trends. Earlier studies from the mid-2000s primarily described the bacteriology of DFIs using swab-based sampling, while more recent cohorts incorporated deep-tissue sampling, automated identification systems, and standardized AST protocols such as CLSI and EUCAST. The introduction of technologies like VITEK 2 and molecular screening for mecA and ESBL genes has improved accuracy and comparability across studies (Atlaw et al., 2022; Makeri et al., 2023). Nonetheless, the overall research landscape remains skewed toward urban tertiary hospitals, with limited data from rural or primary care settings where diagnostic capacity is weakest and empirical antibiotic use is most common. This concentration of data in higher-level facilities may underestimate the true burden of MDR infections in community settings. Similarly, the exclusion of studies published in languages other than English may have inadvertently impacted representation.

When compared with global data, the magnitude of antimicrobial resistance in African DFIs is considerably higher. MRSA rates exceeding 30% and ESBL detection approaching 50% in Enterobacterales contrast sharply with estimates below 20% in most high-income regions (Makeri et al., 2023; Rigato et al., 2018). These differences reflect structural inequities in antibiotic access and regulation. In many African countries, antibiotics are widely available without prescription, leading to frequent misuse and incomplete treatment courses that accelerate resistance (Ameh et al., 2022). The persistence of MRSA in both hospital and community settings further suggests transmission across multiple care levels, underscoring the need for coordinated infection control practices. The detection of carbapenem-resistant organisms in Egypt and South Africa (Quazi et al., 2025; Salem et al., 2021) also signals an alarming shift toward resistance patterns typically seen in highly industrialized healthcare systems, but occurring in environments with limited treatment alternatives.

Despite these challenges, there are encouraging examples of progress. Studies from South Africa and Egypt demonstrate that the implementation of multidisciplinary diabetic foot clinics, coupled with microbiology-guided antibiotic selection, can significantly reduce amputation rates and improve healing outcomes (Patel et al., 2024; Salem et al., 2021). These findings support calls for the integration of AMR surveillance and stewardship into chronic disease programs. Establishing regional microbiological databases, promoting early referral systems, and scaling up laboratory capacity would help generate timely data for clinical decision-making and policy formulation.

Limitations and Conclusion

This review has several limitations that warrant consideration. The included studies varied widely in sampling methods, case definitions, and laboratory protocols, which limits comparability across settings. Some earlier studies relied on swab cultures rather than deep-tissue sampling, potentially underestimating the presence of anaerobic or fastidious organisms. Variations in antimicrobial susceptibility testing methods

and interpretive criteria, particularly between CLSI and EUCAST standards, may also have influenced resistance estimates. Additionally, few studies employed molecular techniques to confirm resistance mechanisms such as mecA or ESBL gene detection, and many lacked standardized definitions of multidrug resistance. The restriction to English-language publications likely excluded relevant data from francophone and Arabic-speaking regions, leading to underrepresentation of parts of Central and North Africa where DFI research is emerging.

Conclusion

Despite these limitations, this review provides one of the most comprehensive syntheses of the microbiological and clinical dimensions of diabetic foot infections across Africa. The findings demonstrate that multidrug-resistant pathogens, particularly methicillin-resistant Staphylococcus aureus and ESBL-producing Enterobacterales, are now major drivers of infection severity, treatment failure, and poor outcomes. The convergence of high infection burden, limited diagnostic capacity, and empirical antibiotic use underscores the urgency of implementing robust antimicrobial stewardship, strengthening laboratory infrastructure, and expanding access to multidisciplinary diabetic foot care. Policy responses should include integrating wound infection surveillance into national AMR programs, regulating over-the-counter antibiotic sales, and investing in specialized diabetic foot clinics across tertiary hospitals. Addressing these gaps is essential to reduce preventable amputations, improve healing outcomes, and curb the escalating threat of antimicrobial resistance in diabetic wound management across Africa.

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